Anesthesia and Analgesia

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Because the longer procedure raises the surgical risk...

PAVULON®
(pancuronium bromide injection)

Your best choice for 60-plus minutes of dependable relaxation... in every type of patient

Organon Pharmaceuticals
A Division of Organon Inc.
West Orange, N.J. 07052

Please see following page for brief summary of prescribing information.

P24,585

PAVULON®
(pancuronium bromide, injection)

BRIEF SUMMARY
(Please consult package insert for full prescribing information.)

> THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS
> FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.
Cardiovascular: A slight increase in pulse rate is frequently noted.
Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.
Skin: An occasional transient rash is noted accompanying the use of Pavulon.
Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:
2 ml. ampuls—2 mg./ml.—boxes of 25, NDC #0052-0444-26
5 ml. ampuls—2 mg./ml.—boxes of 25, NDC #0052-0444-25
10 ml. vials—1 mg./ml.—boxes of 25, NDC #0052-0443-25

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted except by written consent of the publisher and the author.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

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Subscription information for 1986 applying to IARS members: USA and possessions, $50.00 per year, in all other countries $61.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: Emerson A. Moffitt, MD. Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

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Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York NY 10017. Subscriptions are entered for the calendar year, January–December.

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See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

Anesthesia and Analgesia

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SCIENTIFIC ARTICLES

SUFENTA®
(sufentanil citrate) Injection C II

Available in 1 ml, 2 ml, 5 ml ampoules; boxes of ten.

JANSSEN PHARMACEUTICA

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1986 Awards

The Board of Trustees of the IARS is pleased to advise that four Awards were granted and announced at the March 1986 meeting in Las Vegas, as follows:

Zeljko J. Bosnjak, PhD, Medical College of Wisconsin, Milwaukee, WI:
   "Effects of Chronic Administration of Calcium Antagonists"
John F. Butterworth IV, MD, Bowman Gray School of Medicine, Winston-Salem, NC:
   "Brain Cellular Mechanisms of Increased Anesthetic Susceptibility with Aging"
Philippe R. Housmans, MD, PhD, Mayo Foundation, Rochester, MN:
   "Influence of Halothane on Intracellular Calcium Handling in Mammalian Cardiac Muscle"
Vladimir Nigrovic, MD, Medical College of Ohio, Toledo, OH:
   "Adverse Reactions and Metabolism of Atracurium"

1987 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1987 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.

- The applicant must be a member of the International Anesthesia Research Society.

- Applications must be received in the IARS Cleveland office no later than December 15, 1986.

- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

> International Anesthesia Research Society
> 3645 Warrensville Center Rd.
> Cleveland, OH 44122
>   Telephone: (216) 295-1124

The 1987 Award(s) will be announced at the Annual Scientific Meeting (61st Congress) of the International Anesthesia Research Society to be held at the Buena Vista Palace, Lake Buena Vista (Orlando), Florida, March 14-18, 1987.

Myocardial ischemia is often a major concern in heart failure...

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Now... an inotropic agent that does not increase MVO_2

Instead of catecholamines

for the short-term management of heart failure

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(edrophonium chloride injection, USP)

A rapid-acting neuromuscular reversal agent

From the developers of
Ethrane® (enflurane) **and Forane®** (isoflurane)

60-second reversal
of neuromuscular blockade

- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.[1,2]

- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.[1,2*]

- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 μg/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using *twice* the atropine dose (15 μg/kg).[1,2]

- **May be the preferred reversal agent for atracurium and vecuronium**
"...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade."[3]

"Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."[4]

*Note: When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

Anaquest

introduces

Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:

ENLON contains in each mL of sterile solution:
10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:
Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:
Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:
The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:
Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

NDC 10019-873-15   15 mL multidose vials.   2-85

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A16

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In the past three years, since the introduction of the Nellcor® N-100 pulse oximeter, Nellcor has become one of the fastest growing health-care companies in the U.S.

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The partnership that we have developed with you has helped us to make your high standard of care our standard. We will keep it that way, now and in the future.

We believe that one good turn deserves another.

We want to thank you for your support and at the same time continue our commitment to patient safety through pulse oximetry by giving you a free Nellcor N-100 pulse oximeter for every three units that your hospital purchases, at list price, between May 1st and July 31st.

To take advantage of this program, contact your local Nellcor representative or Nellcor Incorporated, 25495 Whitesell Street, Hayward, California 94545. Toll-free telephone 800 433-1244. (In California 800 351-9754.)

Nellcor. Pulse oximetry for every patient, everytime, everywhere.

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THE SUFENTA® REPORT
A PRACTICAL ANESTHESIA UPDATE
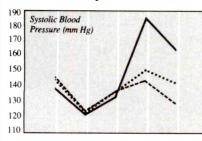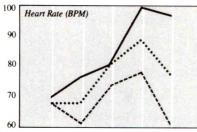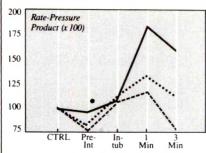
LESS BARBITURATE, BETTER STABILITY WITH LOW-DOSE SUFENTA®

SAN FRANCISCO: Low doses of SUFENTA® (sufentanil citrate) Injection Ⓒ, given prior to thiopental as an adjunct to induction, improved hemodynamic stability and reduced barbiturate requirements, according to a study presented here at the 1985 Annual Meeting of the A.S.A. In a group of 30 adult patients who underwent surgery of 25 min. to 8.5 hr. duration, thiopental was used for induction, either alone or combined with SUFENTA. SUFENTA (0.5 or 1.0 $\mu g/kg$) reduced thiopental requirements by 50% to 68%, respectively, and the hemodynamic response to laryngoscopy and intubation was attenuated, as measured by systolic pressure, heart rate and rate-pressure product. Bradycardia, truncal rigidity and recall were not observed.

Better Hemodynamic Control

Systolic Blood Pressure (mm Hg)

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CTRL Pre-Int In-tub 1 Min 3 Min
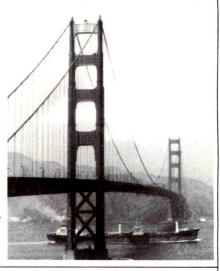
— Thiopental, 10 patients
···· SUFENTA 0.5 $\mu g/kg$ + thiopental, 10 patients
- - - SUFENTA 1.0 $\mu g/kg$ + thiopental, 10 patients

(Abstracted from Brizgys, Morales and Owens, *Anesthesiology* 1985; 63:A377)

Experience With 93 Patients Generates "Thumbnail" Dosage Guidelines

Clinical experience with SUFENTA in general surgery revealed that *total dosage requirements averaged about 1 $\mu g/kg/hour$ or less,* in surgery up to 8 hours.

In the same patients the *induction dose averaged about 75% of total dose.* The remainder was given in incremental maintenance doses as needed.

The induction dose of SUFENTA administered prior to intubation reduces hypertension and tachycardia.

In every case, however, dosage should be titrated to individual patient needs.

NOW SHOWING: AN INFORMATIVE 22-MINUTE FILM

Benjamin J. Kripke, MD, and Edson O. Parker III, MD, are featured in the medical film "SUFENTA: A Practical Guide for General Surgical Procedures." The anesthesiologists demonstrate, through actual hands-on experience, how careful dosage planning provides maximal hemodynamic stability throughout the entire procedure. To arrange a viewing of this film, please contact your local Janssen Representative.

Adult Dosage Recommendations: A Summary

Please see full Prescribing Information, including dosage, on next page.

	General Surgical Procedures	Major Surgical Procedures
Expected Duration	1 to 2 hours	2 to 8 hours
Types of Procedures	Total vaginal hysterectomy, gall bladder surgery, bilateral inguinal hernia repair, open reduction of fractures	Major orthopedic surgery, carotid endarterectomy, nephrectomy, major abdominal surgery (e.g., colectomy)
Recommended Induction Dose	1 to 1.5 μg/kg (1.4 to 2.1 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation	1 to 5 μg/kg (1.4 to 7 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation
Recommended Maintenance Dose	10 to 25 μg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose	10 to 25 μg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose
Total Dosage	For cases lasting 2 hours, would not be expected to exceed 2 μg/kg (2.8 ml for a 70 kg patient) when used with N_2O/O_2	For cases lasting 8 hours, would not be expected to exceed 8 μg/kg (11.2 ml for a 70 kg patient) when used with N_2O/O_2
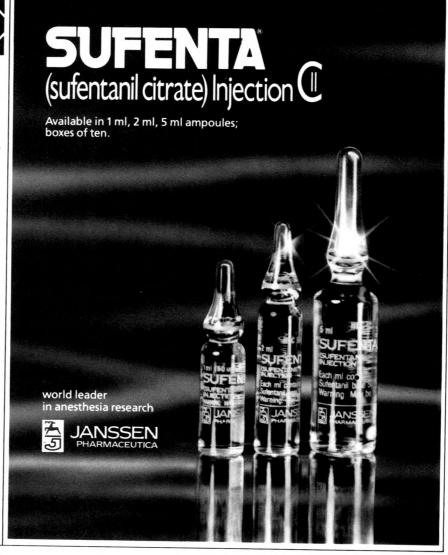
SUFENTA® BRIEFCASE

Putting SUFENTA to Work in Your Practice

In actual clinical practice, when used in balanced general anesthesia, SUFENTA is about 10 times as potent as fentanyl. Thus, 1 ml SUFENTA (50 μg/ml) is equivalent to 10 ml fentanyl (50 μg/ml).

Because of this potency difference, less volume of drug is needed, making it especially convenient for use in cardiovascular surgery and longer procedures. For accurate dosage calibration in shorter procedures, a tuberculin syringe, a 2 ml insulin syringe or dilution may be helpful.

In a laboratory study, SUFENTA has been found to be compatible and stable in solution with 5% glucose in water, 5% glucose in normal saline, lactated Ringer's solution and normal saline (tested in plastic containers refrigerated at 4°-8°C for 24 hours followed by 48 hours at room temperature).

SUFENTA® (sufentanil citrate) Injection Ⓒ II

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxy-methyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1). SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

CLINICAL PHARMACOLOGY: SUFENTA is an opioid analgesic. When used in balanced general anesthesia, SUFENTA has been reported to be as much as 10 times as potent as fentanyl. When administered as a primary anesthetic agent with 100% oxygen, SUFENTA is approximately 5 to 7 times as potent as fentanyl. (See dosage chart for more complete information on the use of SUFENTA.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia; at doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 1.4 minutes, redistribution of 17.1 minutes and an elimination half-life of 164 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA-nitrous oxide/oxygen produced reductions in cerebral blood flow comparable to those of enflurane-nitrous oxide/oxygen. During cardiovascular surgery, SUFENTA-oxygen produced EEG patterns similar to fentanyl-oxygen; these EEG changes were judged to be compatible with adequate general anesthesia.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Skeletal muscle rigidity is related to the dose and speed of administration of SUFENTA. This muscular rigidity may occur unless preventative measures are taken (see Warnings).

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated:
as an analgesic adjunct in the maintenance of balanced general anesthesia.
as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

**WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.
An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.**

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.
Vital signs should be monitored routinely.
Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).
The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.
High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.
Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.
Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.
Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compro-mised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.
Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.
No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.
There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.
Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.
Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.
ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.
The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).
Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia	Dermatological: itching, erythema
Gastrointestinal: nausea, vomiting	Central Nervous System: chills
Respiratory: apnea, postoperative respiratory depression, bronchospasm	Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.
DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).
Vital signs should be monitored routinely.
See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.
Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.
Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.
Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	MAINTENANCE DOSAGE
ADMINISTRATION WITH NITROUS OXIDE/OXYGEN FOR SURGICAL PROCEDURES LASTING UP TO EIGHT HOURS:	
• TOTAL DOSAGE REQUIREMENTS OF 1µG/KG/HR OR LESS ARE RECOMMENDED	
1-2 µg/kg: Expected duration of anesthesia 1-2 hours. Approximately 75% or more of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 µg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.
2-8 µg/kg: Expected duration of anesthesia 2-8 hours. Approximately 50 to 75% of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**10-50 µg (0.2-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
ADMINISTRATION WITH 100% OXYGEN	
8-30 µg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release has been shown to be attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 µg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.
Also see WARNINGS and PRECAUTIONS sections.
For purposes of administering small volumes of SUFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
HOW SUPPLIED: SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01   50 µg/ml, 1 ml ampoules in packages of 10
NDC 50458-050-02   50 µg/ml, 2 ml ampoules in packages of 10
NDC 50458-050-05   50 µg/ml, 5 ml ampoules in packages of 10

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Thoracic Epidural Anesthesia Reduces Myocardial Infarct Size after Coronary Artery Occlusion in Dogs

Richard F. Davis, MD, Lawrence W. V. DeBoer, MD, and Peter R. Maroko, MD

DAVIS RF, DEBOER LWV, MAROKO PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. Anesth Analg 1986;65:711–7.

The effect of thoracic epidural anesthesia (TEA) with lidocaine on regional myocardial blood flow (RMBF), hemodynamic performance, and myocardial infarct size after coronary artery occlusion was assessed in 21 dogs. In seven dogs, the left anterior descending coronary artery (LAD) was temporarily occluded twice: once before TEA (control) and once during TEA. Systemic hemodynamic parameters, RMBF (using radionuclide-labeled microspheres), and epicardial electrocardiographic maps (15 sites) were obtained before and 15 min after each temporary LAD occlusion. Compared with the ischemic period before TEA, the following were decreased during ischemia with TEA: heart rate, ST segment elevation, cardiac index, the peak first time derivative of left ventricular (LV) pressure, LV ten-sion–time index, the rate–pressure product, and LV stroke–work index. Ischemic zone endocardial RMBF was increased from a control value of $26 \pm 6\%$ to $36 \pm 6\%$ of normal during TEA ($P < 0.05$). An additional 14 dogs randomly received either TEA (1% lidocaine, 10 ml/hr) or epidural saline plus 1% lidocaine (10 ml/hr, intramuscularly), beginning 1 hr after LAD occlusion. After 6 hr, the heart was removed and the left ventricle was sectioned parallel to the atrioventricular groove. The infarcts (tetrazolium-stained) were 46% smaller with TEA than with saline, $15.4 \pm 1.8\%$ vs $28.7 \pm 2.3\%$ of the left ventricle ($P < 0.05$). Thus TEA reduced hemodynamic correlates of myocardial O_2 consumption, improved regional (ischemic zone) endocardial perfusion, and reduced the extent of myocardial infarction.

Key Words: HEART, MYOCARDIUM—infarction. ANESTHETIC TECHNIQUES—epidural.

The extent of myocardial necrosis resulting from either an acute myocardial infarction (MI) or experimental coronary artery occlusion is affected by a variety of pharmacologic and physiologic interventions (1). The relationship between coronary artery disease or prior MI and perioperative MI is well established, as is the high mortality rate associated with a perioperative recurrent MI (2–5). Because intraoperative ischemic events are related to perioperative MI (6), it is important to determine the effects of anesthetic agents and techniques on myocardial ischemia and infarction.

Previous clinical and experimental studies have shown that thoracic epidural anesthesia (TEA) decreases heart rate, myocardial contractility, and sys-temic vascular resistance, hemodynamic alterations that indicate decreased myocardial oxygen consumption (7–9). TEA with lidocaine has been reported to improve transmural distribution of regional myocardial blood flow (RMBF) in dogs, especially during ischemia (10). The present investigation was designed to test the hypothesis that continuous TEA with lidocaine would reduce myocardial infarct size and increase RMBF to the ischemic myocardium in a canine model with a standardized coronary artery occlusion.

Materials and Methods

Adult mongrel dogs of either sex were anesthetized with intravenous thiamylal, 15 mg/kg, intubated orotracheally, and mechanically ventilated. Additional doses of thiamylal were administered intravenously to maintain unresponsiveness; muscle relaxants were not used. All relevant institutional policies regarding animal research were followed. The external jugular vein and carotid artery were cannulated with polyethylene catheters for pressure monitoring and blood sampling. Standard ECG lead II was monitored con-

tinuously. The heart was exposed through a left thoracotomy and was suspended in a pericardial sling. The left anterior descending coronary artery (LAD) was dissected proximal to the first major apical diagonal branch and loosely encircled with a ligature at that point. The LAD was then occluded for 10–15 sec by tightening the ligature; dogs in which the cardiac apex failed to become cyanotic during this time were eliminated from the study.

A dorsal incision over the spinous processes of the first and second thoracic vertebrae exposed the laminae. By direct vision, a 17-gauge epidural needle was inserted into the epidural space, and a 19-gauge epidural catheter was advanced 3 cm beyond the tip of the needle; the needle was withdrawn and the catheter sutured in place. Animals were then arbitrarily assigned to one of two groups as described below. Within each group animals were randomly assigned to treatment or control.

Hemodynamics and Electrocardiographic Mapping

In seven dogs catheters were placed into the left atrium, the left ventricle, and the femoral artery for measurement of left ventricular (LV) end-diastolic pressure (LVEDP), and the peak first time derivative of LV pressure (dP/dt). Regional myocardial blood flow and cardiac output (CO) were measured using radionuclide-labeled microsphere techniques (11). The LV pressures were measured with a 12-in segment of fluid-filled, rigid polyethylene tubing connected to a transducer (Statham P23) calibrated to a mercury column with the zero reference set to the level of the left ventricle. The fundamental frequency of this system was 27.8 Hz with a damping coefficient of 0.202 ± 0.015 (SD), as assessed by a snap test (12). The slope of the line manually drawn tangent to the steepest portion of the ascending limb of the LV pressure curve was taken as dP/dt. LVEDP was measured as the nadir of the LV pressure curve after the "a" wave.

Fifteen epicardial locations on the anterior surface of the left ventricle were selected for electrocardiographic (ECG) mapping; each site was located near an epicardial landmark such as an arterial bifurcation to ensure reproducible placement of the electrode. The ECG was obtained by using a unipolar, handheld electrode connected to an ECG amplifier calibrated to a sensitivity of 1 mV/mm; a recorder speed of 25 mm/sec was used (13). Regions adjacent to epicardial dissection or catheters were avoided to prevent ECG artifact from traumatic epicardial injury. The ST segment elevation (TP segment) was measured 0.04 sec after the end of the QRS complex. Epicardial sites were not used when the QRS was

longer than 0.065 sec because epicardial ST segment elevation as an index of ischemia.is invalidated by intraventricular conduction abnormalities (14). The ECG data are expressed both as the sum of ST segment elevations from each site in mV (Σ-ST) and as the number of epicardial sites with ST elevation greater than 1 mV (N-ST) (13).

After hemodynamic and ECG mapping data were obtained, the LAD was occluded with the previously placed ligature for 15 min. Hemodynamic and ECG measurements were repeated, and microspheres were injected for RMBF calculation, during ischemia. The heart was then reperfused for 1 hr, after which measurements were repeated.

When data were obtained after reperfusion, 10 ml of 1% lidocaine was injected into the epidural catheter; 30 min later, hemodynamic and ECG measurements were repeated again. Then the LAD was occluded again as before and, 15 min later (during ischemia), all measurements were obtained again, and a second set of microspheres injected for RMBF calculation.

Infarct Size

In 14 dogs, the LAD was occluded permanently and the chest closed. Anesthesia, intubation, and mechanical ventilation followed the preceding protocol. One hour after LAD occlusion, either 10 ml of 1% lidocaine ($n = 7$) or normal saline ($n = 7$) was infused via the epidural catheter. Animals receiving epidural saline also received concurrent intramuscular (hind leg) injections of 10 ml of 1% lidocaine. These treatments were repeated hourly in both subgroups for 6 hr, during which lactated Ringer's solution, 8 ml·kg^{-1}·hr^{-1}, was infused intravenously. Heart rate and arterial pressure were recorded continuously. Lead II ECG was evaluated hourly for the severity of ventricular ectopy, which was assigned an arbitrary value of 1 (no ectopy), 2 (<six premature ventricular contractions/min), 3 (>six PVC/min), or 4 (ventricular tachycardia). Animals developing ventricular fibrillation after LAD occlusion were excluded from the study.

After 6 hr, a lethal dose of sodium pentobarbital was injected. The hearts were removed, and the distance from the LAD aortic ostium to the site of occlusion was measured with a calibrated probe. Infarct size was determined as previously described (11), except planimetry was done with an electronic digitizer (Hewlett–Packard model # 9111A), and mid-myocardial dimensions for infarcted and normal tissue were not measured.

Arterial blood was sampled hourly after LAD oc-

Table 1. Effects of Transient Coronary Artery Occlusion with and without Concomitant Thoracic Epidural Anesthesia

	Control			Thoracic epidural anesthesia	
	Before ischemia	During ischemia	After 60 min of reperfusion	Before ischemia	During ischemia
Heart rate (beats/min)	129 ± 6	138 ± 5	145 ± 6	113 ± 7^a	112 ± 8^{a,b}
Mean arterial pressure (mm Hg)	104 ± 6	98 ± 8	106 ± 5	93 ± 4^{a,b}	93 ± 5^a
Left ventricular end-diastolic pressure (mm Hg)	5 ± 0.4	5 ± 0.6	5 ± 0.4	4 ± 0.7	6 ± 0.6
Peak LV dP/dt (mm Hg/sec)	2240 ± 302	2024 ± 122	2469 ± 317	2044 ± 331^{a,b}	1666 ± 153^{a,b}
LV tension time index (mm Hg·sec·min^{-1})	2368 ± 310	2276 ± 208	2631 ± 172	1927 ± 195^a	1906 ± 204^{a,b}
Rate–pressure product (beat·min^{-1}·mm Hg) (10^3)	14.3 ± 1.2	14.1 ± 1.1	17.1 ± 1.1	11.4 ± 0.9^{a,b}	11.4 ± 1.1^{a,b}
Σ·ST segment (mV)	0	56 ± 11	0	0	18 ± 8^b
N·ST (sites)	0	8.1 ± 0.7	0	0	1.7 ± 0.9^b

Values are means ± SEM, $n = 7$.
$^a P < 0.05$ when compared with reperfusion value before epidural.
$^b P < 0.05$ when compared with corresponding control.

Table 2. Effects of Thoracic Epidural Anesthesia on Systemic Hemodynamics during Coronary Artery Occlusion

	Control	Epidural
Cardiac index (L·min^{-1}·m^{-2})	2.4 ± 0.3	1.8 ± 0.3^a
Stroke volume index (ml·beats^{-1}·m^{-2})	21.1 ± 1.8	20.7 ± 3.2
Left ventricular stroke work index (g·m^{-1}·beat^{-1})	27.4 ± 3.2	20 ± 3.2^a
Systemic vascular resistance (mm Hg·L^{-1}·min)	46 ± 7	59 ± 9^a

Values are mean ± SEM, $n = 7$.
$^a P < 0.05$ when compared with control.

clusion from three dogs in each subgroup for measurement of plasma lidocaine concentrations and blood gas tensions. Also in these six animals, transmural samples of normal and infarcted myocardium were taken, after infarct size measurements, for measurement of tissue lidocaine concentrations. Arterial blood gas tensions were measured by standard electrode techniques. The blood samples for lidocaine concentration analysis were kept on ice until centrifuged; the plasma fraction was separated and kept frozen (as were tissue samples) for subsequent analysis. Lidocaine assays were done according to a modification of the technique of Keenaghan (15).

Statistics

For both protocols, data from individual dogs were pooled to enable statistical comparisons. Comparisons between subgroups were made by using Student's t-test for grouped data; data obtained over time

within each group were compared by analysis of variance. In the hemodynamic and ECG study, data from the control ischemic state were compared with corresponding data obtained during TEA by using Student's t-test for paired data. The two measurements of infarct size (planimetry and tissue weight) were compared by using least squares linear regression analysis. Results are expressed as mean values ± SEM. A probability of chance occurrence less than 5% ($P < 0.05$) was considered significant.

Results

Hemodynamics and Electrocardiographic Mapping

TEA alone (before coronary artery occlusion) decreased heart rate, mean arterial pressure, LV dP/dt, LV tension–time index, and rate–pressure product (Table 1). There was a marked decrease in both the number of epicardial sites with ST segment elevation (N-ST) and the total magnitude of ST segment elevation (Σ-ST) during ischemia with TEA compared with during control ischemia.

Cardiac index decreased significantly more during ischemia with TEA than during control ischemia; this was heart rate-related because stroke volume index was unchanged (Table 2). Because heart rate decreased, diastolic filling time increased 12.8 ± 3.6% from 36.7 ± 1.4 to 41.2 ± 1.1 sec/min during control and during TEA ischemic periods ($P < 0.05$). Systemic vascular resistance was higher during ischemia with TEA than during control ischemia. Ischemic zone endocardial RMBF was 28% higher with TEA than without TEA (Table 3), but neither ischemic epicardial nor transmural RMBF varied. The endocardial-to-epicar-

Table 3. Effect of Thoracic Epidural Anesthesia on
Regional Myocardial Blood Flow (RMBF) during Coronary
Artery Occlusion

	Control	Epidural
Endocardial RMBF (ml·min^{-1}·100 g^{-1})		
Normal	86 ± 9	79 ± 6
Ischemic	21 ± 5	27 ± 5*
Ischemic (% normal)	25.6 ± 6.3	35.6 ± 6.0*
Epicardial RMBF (ml·min^{-1}·100 g^{-1})		
Normal	82 ± 4	76 ± 6
Ischemic	38 ± 6	37 ± 7
Ischemic (% normal)	47 ± 7	48 ± 9
Transmural RMBF (ml·min^{-1}·100 g^{-1})		
Normal	82 ± 4	76 ± 7
Ischemic	30 ± 5	33 ± 6
Ischemic (% normal)	36 ± 7	43 ± 7
Endocardial-to-epicardial ratio		
Normal	1.03 ± 0.03	0.99 ± 0.03
Ischemic	0.54 ± 0.08	0.79 ± 0.10*

Values are mean ± SEM, n = 7.
*P < 0.05 when compared with control.

Figure 1. Myocardial infarct size with thoracic epidural anesthesia
(circles) and without it (triangles) determined by planimetry and
expressed as percent of left ventricle (LV) as related to infarct size
measured by tissue weight and similarly expressed; the relationship
is given by the regression equation: planimetry = 1.00 (tissue weight)
−1.35, where r = 0.94, SEE = 3.10, n = 14 (P < 0.05).

dial RMBF ratio of the ischemic region increased dur-
ing TEA (Table 3).

Coronary vascular resistance in the nonischemic
myocardium (aortic diastolic pressure minus LVEDP
divided by RMBF) was 1.12 ± 0.14 resistance units
in control studies and 1.17 ± 0.14 during TEA (P >
0.05). Coronary vascular resistance for collateral flow
into the ischemic myocardium (aortic diastolic pres-
sure minus LVEDP divided by ischemic zone trans-
mural RMBF) was 4.31 ± 1.32 resistance units for
control and 3.35 ± 0.83 during TEA (P > 0.05).

Infarct Size

Measured by weight of tissue and expressed as a per-
cent of total LV weight, infarct size in the TEA group
was 16.7 ± 1.9% and, in the control group, 30.0 ±
1.4% (P < 0.05); corresponding values obtained by
planimetry were 15.4 ± 1.8% and 28.7 ± 2.3% for
TEA and control, respectively (P < 0.05). The distance
between the left coronary aortic ostium and the site
of LAD occlusion was 2.6 ± 0.2 cm for both groups.
The relationship between the two infarct size mea-
surement techniques is given by the following equa-
tion: planimetry = 1.00 (tissue weight) − 1.35, where
r = 0.94, SEE = 3.10 (P < 0.05; Fig. 1). The epicardial
extent of the infarct was greater in the control group
than in the TEA group (20.2 ± 3.0% vs 12.2 ± 1.8%
of epicardial circumference, respectively; P < 0.05;
Fig. 2). Results were similar for the endocardium (36.2
± 5.2% vs 23.2 ± 2.6% for control and TEA, respec-
tively; P < 0.05; Fig. 2).

In the infarct size protocol, TEA significantly re-
duced heart rate as compared with the control group,
though mean arterial pressure in the two groups did
not differ significantly (Fig. 3). TEA dogs had less
severe ventricular ectopy than did control dogs; ar-
rhythmia score at 6 hr after LAD occlusion was
3.4 ± 0.4 in control dogs and 1.7 ± 0.4 in TEA dogs
(P < 0.05).
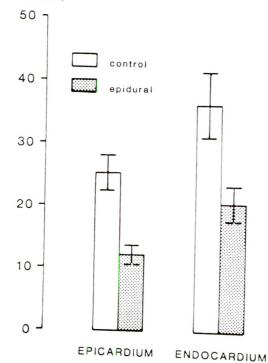
Arterial blood gas analyses during the 6-hr infarc-
tion revealed a mean PaO_2 of 113 ± 8 mm Hg (range
84–243) with 96.9 ± 0.26% hemoglobin saturation in
control animals, and 122 ± 9 mm Hg (range 90–239)
with 97.1 ± 0.21% hemoglobin saturation in TEA an-
imals (P > 0.05). $PaCO_2$ was 31 ± 1 mm Hg (range
24–45) in control and 39 ± 2 mm Hg (range 30–60)
in TEA (P < 0.05); and pH was 7.38 ± 0.02 (range
7.24–7.50) in control and 7.30 ± 0.02 (range 7.11–7.41)
in TEA (P < 0.05).

Neither plasma nor myocardial concentrations of
lidocaine in TEA dogs were different from those in
control dogs at any time point observed. Lidocaine
concentration in ischemic myocardium was 38% of
that in nonischemic myocardium (range 33–43%) in
control dogs, a value not significantly different from
that in TEA dogs, 34.3% (range 19–50%). Plasma lid-
ocaine concentrations were not significantly different
in TEA dogs from those in control dogs (2.48 ± 0.33
μg/ml vs 1.91 ± 0.46 μg/ml) (P > 0.05), considering
all values obtained over the 6-hr infarction period.

INFARCT SIZE

(% of circumference)

Figure 2. The percent of the circumference of the endocardial surface occupied by infarction in control animals was 36.2 ± 5.2% ($n = 7$) and in thoracic epidural animals was 20.2 ± 3.0% ($n = 7$). For the epicardial surface, corresponding data are 25.2 ± 2.6% for control and 12.2 ± 1.8% for thoracic epidural animals ($P < 0.05$, for both comparisons).

Discussion

When compared with epidural saline and intramuscular lidocaine injections, TEA with lidocaine markedly decreased myocardial ischemic injury and infarct size. Blood and myocardial lidocaine concentrations did not differ between the two groups; therefore lidocaine per se, which has been reported to reduce myocardial ischemia (16), was unlikely to have been the significant factor in these results. Likewise, the groups did not differ significantly in PaO_2 or oxyhemoglobin saturation. Although $PaCO_2$ was greater and pH lower in TEA dogs than in control dogs in the infarct size protocol, the actual differences were small and the ranges largely overlapped. Therefore it is unlikely that either systemic oxygenation or acid base balance influenced the differences in myocardial ischemia between the groups.

The decreased myocardial ischemia (i.e., decreased ST segment elevation and decreased infarct size) was associated with hemodynamic changes that decrease myocardial oxygen consumption (17), namely nega-

tive inotropic and negative chronotropic effects. However, with regard to LV dP/dt, an index of contractility, the catheter–transducer system used to measure LV pressure was relatively underdamped and had a relatively low fundamental frequency. Therefore, absolute values of LV dP/dt should be interpreted cautiously, although the relative changes between time periods are reliable.

The RMBF data indicate that increased ischemic subendocardial flow may have decreased ischemic injury in association with TEA, although endocardial salvage was not greater than epicardial salvage. The increased endocardial (ischemic zone) RMBF could have been due to an increase in diastolic filling time (reduced heart rate) or a decrease in the resistance to collateral flow into the ischemic zone. The significantly increased diastolic filling time and the stability of both collateral resistance (as calculated) and ischemic zone transmural RMBF indicate that the heart rate was more important.

These results agree with previous investigations. A cervicothoracic epidural anesthetic technique, similar to that in the present investigation but with experimentally controlled coronary blood flow, increased endocardial-to-epicardial blood flow ratio in dogs, especially during ischemia, but decreased systemic arterial pressure and increased coronary vascular resistance in normally perfused regions (10). The hemodynamic effects of TEA contribute to the reduced ischemia since restoration of mean aortic pressure (with phenylephrine) and heart rate (by atrial pacing) to preepidural control values negated that reduction (9). Data from the present investigation document a smaller infarct size with TEA, with transmural myocardial salvage.

TEA may have inhibited cardiac sympathetic innervation and thus may have decreased ventricular ectopy. Whereas selective blockade of the right stellate ganglion increases the risk of ventricular ectopy during ischemia (18), either selective left stellate ganglion blockade or complete cardiac sympathectomy has prevented ventricular ectopy produced by ischemia (19). Also, the decreased ventricular ectopy in this study may have contributed to the slower heart rate during TEA and thus to the reduced ischemia.

The significance of sympathetic innervation of the coronary vasculature as a tonic control of coronary vascular resistance, coronary blood flow, and distribution of flow is not clear (20). In conscious dogs, a resting sympathetic constrictor tone was shown in the coronary circulation and was attenuated by carotid sinus (not cardiac sympathetic) nerve stimulation (21). Both reactive hyperemia and endocardial-to-epicardial blood flow ratio are increased by left (but not by
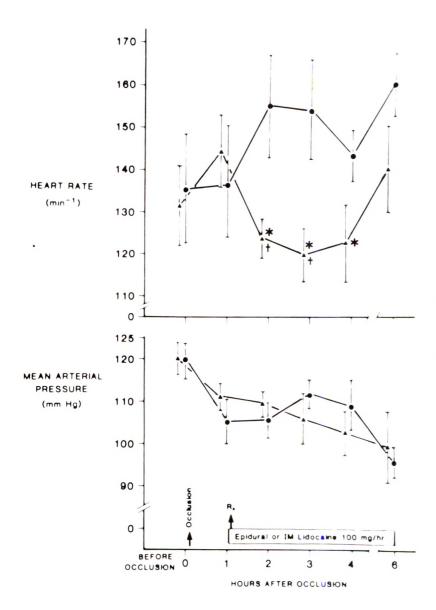
Figure 3. The comparison of heart rate and mean arterial pressure data from infarct size studies in dogs treated with (triangles, $n = 7$) or without (circles, $n = 7$) thoracic epidural anesthesia (TEA) shows no significant differences in arterial pressure but a significant decrease in heart rate with TEA. Asterisk indicates $P < 0.05$ when compared with corresponding control (without epidural) values and dagger indicates $P < 0.05$ when compared with pretreatment values.

right) stellate ganglionectomy; moreover, the effect of left stellectomy is mimicked by the administration of phentolamine, although phentolamine has no effect after stellectomy (22). Coronary blood flow distal to an LAD stenosis is reduced during left sympathetic stimulation, and this is associated with systolic dyskinesis of the anterior LV wall, decreased LV tension, and ST segment elevation (23). In the anesthetized cat, myocardial ischemia per se has increased spontaneous activity in the cardiac sympathetic nerves (24). Therefore, a reduction in α-adrenergic tone mediated by the left stellate ganglion increases the potential for coronary vasodilation in response to ischemia, whereas sympathetic stimulation has the opposite effect.

The use of the anesthetized dog deserves comment. When compared with the conscious dog, the

barbiturate-anesthetized dog has an elevated heart rate and arterial pressure (25). Moreover, the neural control of coronary vascular reactivity may differ between the two states, as does the response of the renal vasculature to graded hemorrhage (26). However, the coronary blood flow response to heart rate change and to carotid sinus nerve stimulation has been shown to exist during barbiturate anesthesia (27,28).

The hemodynamic effects of TEA observed in this study are those of a cardiac sympathetic blockade, although this was not specifically documented. The epicardial ECG data and the infarct size data document less myocardial ischemia and infarction in association with TEA. The regional blood flow studies show that endocardial RMBF and the endocardial-to-epicardial RMBF ratio in ischemic myocardium increased. Whether these effects significantly benefited

the ischemic myocardium beyond the systemic hemodynamic effects of TEA or simply were functions of the increased diastolic filling time remains to be established. Also, the epidural spread of local anesthetic may have produced other systemic effects. Although total sympathetic blockade would seem unlikely with the systemic vascular resistance effects of TEA (Table 2), there may have been partial visceral sympathectomy, which could have reduced the sympatho-adrenal "stress" response to myocardial ischemia and/or to the surgical preparation, thereby decreasing the myocardial ischemia. Further studies with more specific interventions directed at the cardiac sympathetic nerves are required to make these distinctions.

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Intrathecal Morphine and Heroin in Humans:

Six-Hour Drug Levels in Spinal Fluid and Plasma

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KOTOB HIM, HAND CW, MOORE RA, EVANS PJD, WELLS J, RUBIN AP, McQUAY HJ. Intrathecal morphine and heroin in humans: six-hour drug levels in spinal fluid and plasma. Anesth Analg 1986;65:718–22.

Lumbar spinal fluid and plasma concentrations of morphine were measured by radioimmunoassay after intrathecal administration of 1 mg of morphine (n = 13) or heroin (n = 10). Plasma levels of morphine were measured regardless of 'whether heroin or morphine was injected intrathecally, because of the rapid biotransformation of heroin to morphine in plasma. Significant drug concentrations appeared in plasma after intrathecal heroin (peak concentration 47.8 ± 9.0 nmol/L, time to peak concentration 10 ± 2.4 min); after intrathecal morphine plasma drug concentrations were significantly lower (8.1 ± 1.0 nmol/L; P < 0.002) and significantly later (216 ± 39 min; P < 0.002). Elimination half-life of heroin from spinal fluid (43 ± 5 min) was significantly shorter than for morphine (73 ± 5 min; P < 0.02).

Key Words: ANALGESICS—morphine, heroin. ANESTHETIC TECHNIQUES—spinal. PHARMACOKINETICS—morphine, heroin.

Intrathecal injection of 1 mg of morphine can produce almost complete relief of postoperative pain (1,2) that lasts for about 1 day in patients undergoing total hip replacement (3). It is likely that the analgesia produced by intrathecal opiate administration is closely related to the maintenance of high cord drug concentrations (4,5). Very large spinal fluid morphine concentrations result from intrathecal administration (5,6); these high spinal fluid levels constitute a reservoir for maintaining high cord morphine concentrations and hence high receptor occupancy.

The way in which spinal fluid morphine and heroin concentrations change in the first 30 min after intrathecal injection has been described (6). Spinal fluid morphine concentrations obtained by a small number of repeated dural punctures have also been reported (7). This study aimed to extend the earlier kinetic treatment of intrathecal morphine and heroin disposition by repeated sampling of spinal fluid from an indwelling catheter for 6 hr.

Patients and Methods

Twenty-three patients undergoing elective major orthopedic surgery at the Charing Cross Hospital, London, were studied; patients gave informed consent and the investigation was approved by the local ethics committee. Male or female patients over 18 years of age and weighing between 45 and 90 kg were selected; those with clinically apparent hepatic, renal, cardiac, or respiratory disease were excluded from the study.

Anesthesia

Premedication was with 1 mg oral lorazepam. After induction of general anesthesia with thiopental (4 mg/kg), pancuronium (0.1 mg/kg), and atropine (0.6 mg) intravenously, normocapnic ventilation was maintained with nitrous oxide/oxygen (7:3) using a Bain circuit and Nuffield ventilator. Supplementation with halothane (0.5%) was used where necessary to control hypertension or maintain depth of anesthesia. A 16-gauge Tuohy needle was used for dural puncture

at the mid lumbar level, and an 18-gauge catheter with bacterial filter was inserted into the spinal fluid.

Intrathecal Drug Administration

Thirteen patients received 1 mg of preservative-free morphine sulphate pentahydrate (2.64 μmol morphine), and ten patients received 1 mg anhydrous diamorphine (heroin) hydrochloride (2.46 μmol heroin) intrathecally. After the induction of anesthesia, drugs were injected through the spinal catheter, in 5 ml normal saline solution, over a period of 1 min. The catheter was then flushed with 10 ml of the patient's own cerebrospinal fluid (CSF) over a period of 30 sec; CSF samples were collected after discarding the fluid in the catheter. Sample times were taken from the end of the intrathecal injection.

Sampling and Drug Measurement

Simultaneous CSF (2 ml) and peripheral venous blood samples were taken at the time of insertion of the spinal catheter and at 10, 30, 60, 90, 120, 180, 240, 300, and 360 min after the injection of morphine, or at 5, 10, 20, 30, 40, 60, 90, 120, 150, 180, 240, 300, and 360 min after injection of heroin. Cerebrospinal fluid was collected into sterile plastic containers; blood was collected into plastic tubes containing lithium heparin anticoagulant, the specimens centifuged and the plasma decanted.

CSF and plasma were stored frozen until analysis. Both sets of samples were analyzed for morphine or heroin using a radioimmunoassay which had the same cross-reaction to both drugs (8). Deacetylation of heroin to monoacetylmorphine or morphine is known not to occur early after intrathecal injection (6), but in blood, rapid deacetylation occurs (9). Assays therefore measured morphine or heroin in spinal fluid, but only morphine in plasma.

Data Analysis

CSF morphine and heroin concentrations were compared after correction for the small difference in dose; this was done by dividing the observed concentration by the molar dose of drug to give dose-corrected CSF concentrations. The area under the CSF morphine and heroin concentration-time curves (AUC) were calculated for the 6-hr sampling period by the trapezoidal method; division into the dose gave the 6-hr clearance values. Elimination half-lives were calculated from sample points between 30 and 240 min by linear regression analysis.

For plasma morphine concentrations after intrathe-

Table 1. Patient Details

	Morphine	Heroin
n	13	10
Age (yr)	67 ± 2.1	67 ± 3.7
Weight (kg)	71 ± 3.8	62 ± 2.9
Sex ratio (M/F)	4:9	2:8

Values are mean ± SEM. Patients given intrathecal heroin were significantly lighter ($P < 0.05$, Mann–Whitney U-test).

cal morphine or heroin, values for the maximum observed concentration (C_{max}) and time to maximum concentration (T_{max}) were obtained for each patient. The area under the curve of plasma morphine concentration against time for six hr after intrathecal injection was obtained for each patient using the trapezoidal rule. Mean values are given with the standard error of the mean (SEM). Statistical analysis was with the Mann–Whitney U-test.

Results

After intrathecal morphine, CSF samples were obtained from 13 patients and plasma samples from 11 patients. After intrathecal heroin, CSF samples were obtained from eight patients and plasma samples from ten patients. Demographic variables for both sets of patients are given in Table 1.

Spinal Fluid

CSF morphine concentrations after intrathecal injection of 1 mg (2.64 μmol) morphine sulphate pentahydrate decreased from a mean of about 50 μmol/L at 10 min after injection to 2 μmol/L at 360 min. Dose-corrected CSF concentrations are given in Table 2. The mean elimination half-life of morphine from the spinal fluid was 73 ± 5 min, and the mean CSF clearance was 0.69 ± 0.17 ml/min (Table 3).

CSF heroin concentrations after intrathecal injection of 1 mg (2.46 μmol) anhydrous heroin hydrochloride decreased from a mean of 135 μmol/L at 5 min after injection (89 μmol/L after 10 min) to 1.5 μmol/L at 360 min. Dose-corrected CSF concentrations are shown in Table 2; dose-corrected CSF diamorphine concentrations were significantly lower than CSF morphine between 120 and 300 min, but there were no significant differences between the groups at early (10, 30, 60, 90 min) or late (360 min) times after injection. The mean elimination half-life from the spinal fluid after the heroin injection was 43 ± 5 min, and the mean CSF clearance was 0.63 ± 0.06 ml/min (Table 3). The elimination half-life of heroin was significantly ($P < 0.02$) shorter than for mor-

Table 2. Spinal Fluid Morphine and Heroin
Concentrations (μmol·L^{-1}·μmol dose^{-1})

Time (min)	Intrathecal morphine	n	Intrathecal heroin	n
5			54.8 ± 7.4	8
10	18.6 ± 2.4	9	36.3 ± 7.7	7
20			21.0 ± 3.8	8
30	12.6 ± 1.0	12	12.0 ± 2.8	7
40			8.4 ± 1.0	7
60	8.9 ± 0.8	11	7.3 ± 1.0	7
90	6.5 ± 0.6	12	4.3 ± 0.6	7
120	4.7 ± 0.4	13	3.5 ± 0.3^a	8
150			2.2 ± 0.7	8
180	2.8 ± 0.3	11	1.1 ± 0.2^b	
240	1.8 ± 0.2	13	0.47 ± 0.09^b	5
300	1.1 ± 0.1	13	0.51 ± 0.13^c	6
360	0.81 ± 0.10	12	0.62 ± 0.20	4

Values are mean ± SEM.

The intrathecal dose of morphine was 2.64 μmol and of heroin was 2.46 μmol.

^{a}Significant difference between the groups ($P < 0.05$).
^{b}Significant difference between the groups ($P < 0.002$).
^{c}Significant difference between the groups ($P < 0.02$).

phine, but there was no significant difference in clearance.

Plasma

Plasma morphine concentrations after intrathecal morphine and heroin injection are shown in Figure 1 and Table 4. After intrathecal morphine, levels rose slowly; C_{max} was 8.0 ± 1.0 nmol/L, and T_{max} was 216 ± 39 min.

After intrathecal heroin, plasma levels of morphine rose rapidly with a mean C_{max} of 47.8 ± 9.0 nmol/L and T_{max} of 10 ± 2.4 min. Values for C_{max} and T_{max} after intrathecal morphine and heroin were significantly different ($P < 0.02$).

Plasma morphine concentrations were significantly higher after intrathecal heroin than they were after intrathecal morphine for the first 240 min, but not later (Table 4). This was reflected in the significantly ($P < 0.02$) greater AUC of morphine after intrathecal heroin (3503 ± 560 min·nmol·L^{-1}) than it was after intrathecal morphine (1611 ± 192 min·nmol·L^{-1}) over the 6 hr after intrathecal injection.

Discussion

Intrathecal opiate administration provides analgesia of high quality and long duration, and is especially useful for the treatment of postoperative pain in circumstances where patients are cared for in a well-staffed recovery ward after surgery. The fate of intrathecal opiate is one important factor in understand-

Table 3. Spinal Fluid Kinetics of Intrathecal Morphine and Heroin

	Morphine ($n = 13$)	Heroin ($n = 7$)
Clearance (ml/min)	0.69 ± 0.17	0.63 ± 0.06
Elimination t$_{\frac{1}{2}}$ (min)	73 ± 5	43 ± 5^a

Drug clearance over 6 hr was determined by dividing the area under the CSF concentration against time curve into the intrathecal drug dose. Elimination half-life was determined by linear regression analysis of the data points between 30 and 240 min.

^{a}Indicates a significant difference between elimination half-lives ($P < 0.02$, Mann–Whitney U-test).

ing the safe and effective use of this new method for the control of pain.

This study confirms that intrathecal injection of small doses of morphine or heroin results in CSF concentrations that are greater by orders of magnitude than those observed after parenteral morphine administration (6). The use of multiple sampling without repeated dural puncture demonstrates that CSF opiates behave in a coherent and predictable fashion, with small standard error values for CSF drug concentrations and derived kinetic parameters.

The elimination half-life of spinal fluid morphine was about 73 min, which is of the same order as the elimination half-life estimated from short duration multiple sampling (6). A longer elimination half-life of about 180 min (range 150–216 min) has been reported by Nordberg (7). In his study a small number of CSF samples were obtained by multiple dural punctures over about 18 hr. The difference between these present data and those reported by Nordberg may simply reflect artifactual differences that result from a choice of sampling times and the duration of the study (10). In this present study there were indications that elimination became slower after 4 or 5 hr for both morphine and heroin (Table 2). Theoretical considerations indicate that elimination from a small central compartment should eventually assume the rate of the driving compartment, probably plasma (11).

Morphine elimination from the CSF should probably have at least three components: a rapid redistribution phase with a half-life of 1–2 min (6), a long elimination with a half-life of about 80 min as described here, and a more prolonged elimination at spinal fluid concentrations below about 1000 nmol/L, as suggested by the data from Nordberg (7). Conclusive demonstration of this multiexponential elimination would require studies lasting about 1 day with sampling from an indwelling intrathecal catheter.

A similar multiexponential elimination is likely to occur with heroin, with an initial rapid distribution phase with a half-life of 1–2 min, a longer elimination
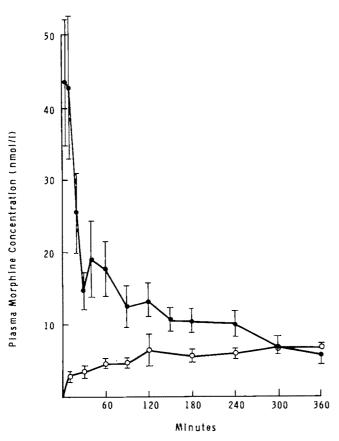
Figure 1. Mean plasma morphine concentrations (± SEM) after intrathecal injection of 1 mg (2.64 μmol) morphine sulphate pentahydrate (○) or of 1 mg (2.46 μmol) anhydrous heroin hydrochloride (●).

Table 4. Plasma Morphine Concentrations (nmol/L) after Intrathecal Morphine and Heroin

Time (min)	Intrathecal morphine	n	Intrathecal heroin	n
5			43.5 ± 8.7	10
10	2.3 ± 0.5	11	42.8 ± 10.1[a]	10
20			25.5 ± 5.5	9
30	2.4 ± 0.4	10	14.6 ± 2.6[a]	9
40			19.2 ± 5.1	10
60	4.1 ± 0.5	11	17.7 ± 3.8[a]	9
90	4.1 ± 0.3	11	12.5 ± 2.9[a]	10
120	4.8 ± 0.5	10	13.4 ± 2.3[a]	8
150			10.7 ± 1.6	7
180	5.0 ± 0.5	10	10.5 ± 1.6[b]	6
240	5.7 ± 0.7	10	10.2 ± 1.8	5
300	6.7 ± 1.0	10	7.2 ± 1.3	•6
360	6.3 ± 1.2	9	5.9 ± 1.4	4
AUC	1611 ± 192	11	3503 ± 560[a]	10

Values are mean ± SEM.

The intrathecal dose of morphine was 2.64 μmol and of heroin was 2.46 μmol. As heroin is rapidly transformed to morphine in plasma, plasma levels of morphine were measured regardless of whether morphine or heroin was injected intrathecally.

[a]Significant difference between the groups ($P < 0.002$).

[b]Significant difference between the groups ($P < 0.02$).

with a half-life of about 45 min, and an even more prolonged elimination at low spinal fluid concentrations. The final elimination half-life would probably be that of morphine, reflecting elimination of morphine produced by deacetylation in the spinal cord (12).

The exact fate of drugs injected intrathecally is not known. Drugs may move rostrally in the spinal fluid, but Nordberg (7) has calculated that bulk flow through the subarachnoid villi could not account for the speed of morphine elimination from spinal fluid. Morphine probably diffuses across the dura, but will not do so at any appreciable rate (13). The most likely method of morphine and heroin elimination from CSF is by diffusion into the cord and subsequent sequestration by the cord blood supply (4). This is supported by the rapid appearance of drug in the systemic circulation after intrathecal injection; lipophilicity enhances this process (Fig. 1).

Morphine appeared in the blood slowly after the intrathecal injection of morphine, with peak mean plasma concentrations at 300 min. Even then, mor-

phine concentrations were some 500 times greater in CSF than plasma, and evidently a large CSF/plasma morphine concentration gradient existed for many hours after intrathecal administration. The dose-related peak plasma morphine concentration (3.0 nmol·L^{-1}·μmol drug^{-1}) found in this study was similar to that in an earlier study using a 2.5 mg dose (2.9 nmol·L^{-1}·μmol drug^{-1}), (14). Use of very high intrathecal doses of 15 mg morphine can result in a more rapid appearance of morphine in plasma (15), perhaps by mechanisms other than simple cord blood sequestration.

Plasma morphine concentrations were measured after intrathecal heroin because heroin is rapidly deacetylated to morphine in plasma. Plasma morphine levels after intrathecal heroin were very different than those after intrathecal morphine (Table 4, Fig. 1). They were very much greater at early sampling points; C_{max} was about six times higher when corrected for dose, and T_{max} was at 10 min, compared with 216 min for morphine. Plasma morphine concentrations of about 43 nmol/L that occurred 5–10 min after intrathecal injection were appreciable, and this may contribute a supraspinal component to both analgesia and side-effects, as with extradural opiate use (4,5).

Heroin is about 100 times more lipophilic than morphine (16), and the differences in plasma kinetics after intrathecal injection reflect that difference. Indeed, plasma morphine concentrations after intrathecal injection of heroin had values for C_{max} and T_{max} similar

Table 5. Comparison of Plasma Kinetics after Intrathecal and Extradural Morphine and Heroin

	n	C_{max} (nmol·L^{-1}·μmol dose^{-1})	T_{max} (min)
Morphine			
Intrathecal lumbar	13	3.0 ± 0.4	216 ± 39
Extradural lumbar	12	12.7 ± 2.8	7.2 ± 0.9
Extradural thoracic	12	12.3 ± 2.0	< 10
Heroin			
Intrathecal lumbar	8	19.4 ± 3.7	10.0 ± 2.4
Extradural lumbar	7	42.8 ± 13.7	4.7 ± 0.6
Extradural thoracic	12	29.0 ± 5.3	< 5

Values are mean ± SEM. Comparison data for lumbar and thoracic extradural morphine and heroin are from Watson et al., 1984 (18).

to those observed after extradural injection (Table 5). For morphine there were great differences for the values for C_{max} and T_{max} between extradural and intrathecal administration, with intrathecal injection giving much lower values for C_{max} and longer duration for T_{max}.

This comparison emphasizes that lipophilicity is an important determinant of CSF opiate elimination after intrathecal injection. More lipophilic drugs will leave the CSF more rapidly and enter the blood faster. There will be less opportunity, therefore, for lipophilic opiates to move rostrally in the CSF, and this may result in fewer side effects. In principle this suggests that lipophilic opiates should produce less prolonged analgesia than that given by morphine.

There may, however, be other circumstances that alter this conclusion; some lipophilic opiates (such as buprenorphine) (17) may bind to opiate receptors for extended periods, obviating the need for a reservoir of drug in the CSF. Heroin is another special case; although it is removed from CSF more rapidly than morphine it may suffer deacetylation within the spinal cord to produce analgesic duration indistinguishable from that of morphine (3).

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Wakefulness during Cesarean Section after Anesthetic Induction with Ketamine, Thiopental, or Ketamine and Thiopental Combined

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SCHULTETUS RR, HILL CR, DHARAMRAJ CM, BANNER TE, BERMAN LS. Wakefulness during cesarean section after anesthetic induction with ketamine, thiopental, or ketamine and thiopental combined. Anesth Analg 1986;65:723–8.

Thirty-six pregnant women (ASA class I or II) at term who underwent general anesthesia and cesarean section received either ketamine, 1 mg/kg (n = 12); thiopental, 4 mg/kg (n = 13); or a combination of ketamine, 0.5 mg/kg, and thiopental, 2 mg/kg (n = 11). A blood pressure cuff inflated to 250 mm Hg isolated one arm from the effects of succinylcholine so that awareness during anesthesia could be assessed by asking the patient to move her hand. Although only one patient receiving ketamine responded to commands during anesthesia, 46% of patients receiving either thiopental or the combination responded to commands intra-operatively. No patient hallucinated, the incidence of dreams was low (11%), and no postoperative dysphoria was noted. Three patients (8%) had postoperative recall of intraoperative awareness; one had received thiopental and two the combination. Maternal intraoperative cardiovascular responses among the groups were similar, as were umbilical blood gas values, newborn Apgar scores, and neonatal neurobehavioral test scores at 4 and 24 hr. Ketamine more effectively blocked maternal responsiveness to commands and strong stimuli during the first few minutes after anesthetic induction for cesarean section than did thiopental or a combination of thiopental and ketamine, each at a lower dose.

Key Words: ANESTHESIA—obstetric. ANESTHETICS, INTRAVENOUS—ketamine, thiopental.

General anesthesia for cesarean section is usually induced with thiopental. Although it is generally safe and reliable, thiopental does have deficiencies. It readily crosses the placenta and, if administered to the mother in doses higher than 4 mg/kg, can produce significant neonatal depression (1,2). In doses of 4 mg/kg or less, thiopental frequently produces only a brief period of maternal unconsciousness, which may not be sufficient to block awareness to laryngoscopy or surgery (3).

Ketamine has been suggested as an alternative to thiopental. In doses of 1 mg/kg, ketamine is similar to thiopental with respect to maternal cardiovascular response to induction and neonatal neurobehavioral scores (2,4). At this dosage, dysphoria and intraoperative awareness are reported to be low (5). Nonetheless many physicians avoid ketamine because of its reputation for causing dysphoria. Continued concern about maternal intraoperative awareness and dysphoria has led to the suggestion that a combination of thiopental and ketamine, each at a reduced dosage, be used. We assessed the effects of anesthetic induction with ketamine, thiopental, or a combination of the two drugs on maternal intraoperative awareness, recall, dreams, hallucinations, dysphoria, cardiovascular stability, fetal blood gas tensions, and Apgar and neurobehavioral scores of newborns.

Materials and Methods

According to an experimental plan approved by the institutional review board, 36 women (ASA class I or II) at term who were scheduled for elective cesarean section and general anesthesia were assigned by a randomized code to receive either ketamine (1 mg/kg), thiopental (4 mg/kg), or a combination of ketamine (0.5 mg/kg) and thiopental (2 mg/kg) for anesthetic induction. Patients with a history of hypertension, diabetes, preeclampsia, or morbid obesity were excluded, as were women with signs of fetal compromise. To obtain baseline values for blood pressure and

Table 1. Demographics of the Study Groups

	Ketamine ($n = 12$)	Thiopental ($n = 13$)	Combination ($n = 11$)
Age (yr)	23.5 ± 5.3	23.5 ± 4.5	25.5 ± 5.2
Weight (kg)	75.9 ± 17.6	78.9 ± 17.0	71.7 ± 11.3
Blood pressure (mm Hg)			
Systolic	110 ± 8.5*	121 ± 11.8	117 ± 10.5
Diastolic	69 ± 6.6*	75 ± 9.0	72 ± 4.8
Heart rate (beats/min)	87 ± 9.1	84 ± 11.4	84 ± 6.2
Induction to delivery interval (min)	11.5 ± 3.0	11.7 ± 5.2	11.6 ± 4.4

Values are means ± SD.
*Different from thiopental and combination groups ($P < 0.05$).

heart rate, blood pressure measurements obtained in the prenatal clinic were averaged, as were measurements of blood pressure and pulse rate obtained during hospitalization but before cesarean section.

Preoperatively, all patients received 30 ml of 0.3 M sodium citrate. The patients were positioned with left uterine displacement, and ECG and a temperature probe were applied. An automatic oscillometric blood pressure monitor (Sentron, Bard Biomedical) recorded systolic and diastolic blood pressures and heart rate every minute (6). To assess intraoperative awareness, a tourniquet was applied to the arm not used for blood pressure measurement or intravenous infusion and was inflated before the administration of succinylcholine chloride. Thus motor function was maintained in one arm.

Before induction, five determinations of blood pressure and heart rate were obtained, each 2 min apart, and were averaged to obtain the preinduction blood pressure and heart rate. Subsequently 100% O_2 was administered by mask for 5 min; 2 min before anesthetic induction, d-tubocurarine chloride (0.07 mg/kg) was given intravenously. Anesthesia was induced according to drug assignment with either thiopental (4 mg/kg intravenously), ketamine (1 mg/kg intravenously), or a combination of thiopental (2 mg/kg intravenously) and ketamine (0.5 mg/kg intravenously). The tourniquet was inflated to a pressure (250 mm Hg) exceeding systolic blood pressure and succinylcholine chloride (2 mg/kg intravenously) was given. Cricoid pressure was maintained until the trachea was intubated. The lungs were ventilated at a tidal volume of 12 ml/kg and a respiratory frequency of eight breaths/min with 70% N_2O in O_2 (10 L/min total flow), and paralysis was maintained by continuous infusion of succinlycholine chloride (2 mg/min). Blood pressure and pulse rate were measured when the endotracheal tube was inserted and when the skin was incised. After delivery, fentanyl (100 μg, intravenously) was given.

A peripheral nerve stimulator was attached to the

arm isolated from the effects of the muscle relaxant and was used to confirm the maintenance of motor function. To assess awareness, the patient was commanded to squeeze the investigator's hand a specified number of times. If the patient promptly squeezed the investigator's hand the appropriate number of times, the command was repeated but a different number specified. Only if the patient responded correctly both times was a positive response noted. This test was repeated at 30-sec intervals beginning 1 min after injection of the induction agent until delivery. After delivery, the tourniquet was deflated.

The initial status of each newborn was assessed by obtaining umbilical arterial and venous blood gases. Apgar scores were assigned by pediatricians not associated with the study and unaware of the study drug. The babies were later evaluated at 4 and 24 hr after delivery by neonatal neurobehavioral testing conducted by a pediatrician (C.M.D.) trained in the technique and unaware of the test drug (7).

While recovering from the effects of anesthesia, patients were observed for signs of dysphoria by recovery room nurses unaware of the test drug. After the patients had awakened fully, they were asked a standardized set of questions to evaluate the occurrence of dreams, hallucinations, and dysphoria. The same questions were repeated on the day after surgery. To assess recall, patients were asked if they remembered anything from during their operation. Those who indicated they did were then asked to recite the investigator's intraoperative commands. Only those who could were recorded as having had recall.

Analysis of variance was used to compare demographic data, blood pressure values, and fetal blood gas data between groups. Blood pressure changes within groups were compared by using a repeated measures analysis of variance with the Bonferroni correction for multiple comparisons. Comparisons of neonatal Apgar and neurobehavioral scores between groups were performed by using the Kruskal–Wallis statistic. The Fisher–Yates exact probability test was

Table 2. Cardiovascular Effects of Anesthetic Induction

	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)			Heart Rate (beats/min)		
	Ketamine	Thiopental	Combination	Ketamine	Thiopental	Combination	Ketamine	Thiopental	Combination
Before hospitalization	110 ± 10.6	116 ± 10.5	110 ± 5.7	66 ± 8.2	70 ± 7.9	63 ± 9.6	—	—	—
During hospitalization but before cesarean section	109 ± 8.5	121 ± 11.8	118 ± 10.5	69 ± 6.6	75 ± 9.0	72 ± 4.8	87 ± 9.1	84 ± 11.4	84 ± 6.2
Before anesthetic induction	125 ± 13.4	143 ± 12.3[a]	133 ± 9.8	71 ± 12.5	84 ± 8.5	82 ± 10.2	90 ± 11.6	91 ± 11.9	88 ± 16.5
Endotracheal intubation	158 ± 24.7[a]	167 ± 39.8[b]	161 ± 33.1[b]	101 ± 17.3[b]	116 ± 19.0[b]	98 ± 20.9	101 ± 12.0	121 ± 17.8[b]	108 ± 25.9[b]
Incision	147 ± 14.1[b]	163 ± 30.6[b]	156 ± 23.0[b]	95 ± 13.9[b]	100 ± 18.4[b]	96 ± 15.4	103 ± 13.6[b]	112 ± 16.9[b]	105 ± 13.3[b]

Values are means ± SD.
[a] $P < 0.05$ compared with values during hospitalization but before cesarean section within groups.
[b] $P < 0.05$ compared with values before anesthetic induction within groups.

Table 3. Incidence of Positive Responses during Anesthesia

	Incidence of response (n)		
Type of response	Ketamine ($n = 12$)	Thiopental ($n = 13$)	Combination ($n = 11$)
Dreams	0	2	2
Postoperative dysphoria	0	0	0
Followed commands	1[a]	7	4
Reaching movements	0[b]	9	8
Recall	0	1	2

[a] $P < 0.05$ compared with the thiopental group.
[b] $P < 0.05$ compared with the thiopental and the combination groups.

used to compare the incidence of maternal dreams, responsiveness, and recall between groups. A probability of 0.05 or less was considered statistically significant.

Results

The groups were similar with respect to age, weight, preoperative blood pressure, and heart rate (Table 1). With the exception of lower average preoperative systolic and diastolic blood pressures within the ketamine group, none of these measurements differed significantly among the three groups. The lower preoperative blood pressure for mothers in the ketamine group, though statistically significant, was probably a chance occurrence because blood pressure of all groups recorded during prenatal clinic visits did not differ.

Transportation to the operating room had little effect on blood pressure or heart rate (only the increase in systolic blood pressure within the thiopental group was statistically significant) (Table 2). As would be expected, tracheal intubation and incision, which were closely related in time, had the greatest effects on maternal cardiovascular variables. Systolic and diastolic blood pressures increased significantly in all groups ($P < 0.05$), except the combined group, in which the average diastolic blood pressure did not increase significantly. During tracheal intubation or incision, heart rate increased in all groups, although to a lesser extent in the ketamine group.

Responsiveness of patients during anesthesia was divided into two categories: "followed commands," i.e., squeezed the investigator's hand on command the requested number of times, or "made reaching movement," i.e., reached toward her face or the operative site in response to intubation or surgical stimulation. The vigor of reaching movements was surprising and required the investigator to physically restrain the patient's unparalyzed arm to prevent her

Table 4. Responses during Anesthesia

Time after anesthetic induction (min)	Followed commands (%)			Made reaching movement (%)		
	Ketamine ($n = 12$)	Thiopental ($n = 13$)	Combination ($n = 11$)	Ketamine ($n = 12$)	Thiopental ($n = 13$)	Combination ($n = 11$)
1.0	0	15	18	0	31	55
1.5	0	15	18	0	54	64
2.0	8	31	36	0	38	27
2.5	0	31	18	0	38	36
3.0	0	23	18	0	31	18
3.5	0	8	18	0	31	18
4.0	0	15	18	0	0	0
>4.0	0	15	0	0	0	0

from reaching to her face or the surgical field. These movements were easily distinguished from occasional mild spontaneous movements of the nonparalyzed arm, which also were observed.

Only one patient in the ketamine group squeezed the experimenter's hand in response to commands and then only during one 30-sec assessment period. In contrast, when anesthesia was induced with thiopental or the drug combination, almost half of the patients followed commands during anesthesia (Table 3). Most patients who followed commands did so during the first 3 min after induction and responsiveness decreased thereafter; by 7 min after induction, no patient followed commands (Table 4).

Most patients in the thiopental and combination groups exhibited reaching movements after induction, whereas the incidence of reaching movement was statistically lower in the ketamine group (Table 3). The frequency of reaching movement was higher during the first 2.5 min after induction and then decreased rapidly (Table 4). By 4 min after induction, patients no longer responded to the stimulation of either surgery or the endotracheal tube by reaching with their unparalyzed arm. By this time, they had probably received enough N_2O that the stimulation from the endotracheal tube or operation was reduced or eliminated.

The occurrence of hallucinations was judged by whether the patient believed she was asleep (dream) or awake (hallucination) at the time she experienced thoughts or images. None of the women thought they had hallucinated. The overall frequency of dreams was low (11%) and all those who recalled dreams related that they were pleasant. There was no difference in the frequency of dreaming among groups (Table 3). No patients were judged to have had postoperative dysphoria.

Three patients had recall, one in the thiopental group and two in the combined group. Of these, one in the combined group had detailed recall of 3 min of sur-

Table 5. Apgar Scores and Umbilical Blood Gas Values

	Ketamine ($n = 12$)	Thiopental ($n = 13$)	Combination ($n = 11$)
Apgar score ≥ 7 (n)			
1 min	10	13	9
5 min	12	13	10
Umbilical blood gas values (means ± SD)			
Arterial			
pH	7.31 ± 0.04	7.31 ± 0.04	7.32 ± 0.06
P_{CO_2} (mm Hg)	50.5 ± 6.9	50.8 ± 6.7	51.2 ± 10.1
P_{O_2} (mm Hg)	13.8 ± 3.3	15.2 ± 6.3	14.7 ± 4.8
Venous			
pH	7.36 ± 0.05	7.36 ± 0.05	7.38 ± 0.07
P_{CO_2} (mm Hg)	44.6 ± 6.2	44.8 ± 5.9	42.8 ± 7.8
P_{O_2} (mm Hg)	24.3 ± 5.2	25.3 ± 9.6	27.8 ± 5.2

gery beginning 1 min after induction, at which time she had also followed commands. The other two had only fragmentary recollection of the first few minutes of operation. Of these two, one had followed commands and the other exhibited reaching movement. None of the patients who had recall reported pain or said the experience was unpleasant.

The incidence of 1- and 5-min Apgar scores >7 did not differ among groups (Table 5). Likewise, umbilical blood gas data were normal and did not differ among groups. Neurobehavioral scores were judged to be low when responses were absent or weak (0 to 1) and high when responses were fairly brisk or vigorous (2 to 3); the groups did not differ significantly (Table 6).

Discussion

Accounts of intraoperative awareness during general anesthesia range from benign to horrifying (8). Concern that patients should not endure surgery while they are awake and paralyzed has prompted most anesthesiologists to assure that the patient is not aware

Table 6. Neonates with a High Score[a]

	4 Hr after delivery			24 Hr after delivery		
Response	Ketamine ($n = 12$)	Thiopental ($n = 13$)	Combination ($n = 11$)	Ketamine ($n = 12$)	Thiopental ($n = 13$)	Combination ($n = 11$)
Sound	22	10	38	30	40	56
Pinprick	78	80	88	100	100	89
Tone	100	100	88	100	100	100
Rooting	33	40	63	50	90	78
Sucking	67	80	100	100	100	100
Moro	89	100	88	100	90	100
Placing	89	80	88	100	100	100
Alertness	33	30	63	60	100	100
General assessment	89	100	88	100	100	100

[a]High score: response > 1 or general assessment of normal or superior. Values expressed as percentages.

during surgery or does not recall the event or feel pain. On the other hand, to ensure a vigorous newborn infant, the general anesthetic technique commonly employed for cesarean section involves minimal amounts of anesthetic agents before delivery. If incompletely paralyzed, these women frequently move during surgery and on occasion open their eyes. Sometimes they remember major portions of their surgical procedures (9).

Most studies of intraoperative awareness have depended on patient recall. Yet awareness and recall are only partly related because awareness may occur without remembrance (10). Also, studies reveal that a patient can recall an experience but can be unable to verbalize it (11,12). If we had measured awareness by evaluating recall, we would have reported an 8% incidence (3 of 36), which is similar to that reported in other studies (13–15). When we examined the frequency of patients who could follow commands during periods of apparent unconsciousness, we found that almost 30% (12 of 36) were aware enough to respond appropriately. In the thiopental and combined groups, 46% (11 of 24) followed commands. Ketamine significantly reduced this when compared with thiopental. The combination appeared intermediate with perhaps some reduction in awareness as assessed by the ability to follow commands. The criteria for demonstration of awareness were narrow; thus there probably were other patients who were aware but unwilling or unable to respond as commanded (16). Unfortunately, there is no satisfactory way to assess this. Studies to evaluate intraoperative awareness by measuring learning during anesthesia have conflicting results (16,17).

Whereas none of the ketamine group responded to the strong stimuli of intubation and operation by reaching toward the stimulus, over 70% (17 of 24) of the thiopental and combination groups did, which

suggests a greater awareness in these patients. Ketamine may have blocked this response by producing a deeper and longer lasting unconsciousness or by producing enough analgesia that the patients, though partially conscious, did not respond. Alternatively, ketamine could have produced a state wherein the patient, though awake and stimulated, was unable to respond. The stable vital signs in the ketamine group argue against the last explanation.

The critical ketamine dosage appears to be about 1 mg/kg; the lower dosage (0.5 mg/kg), even when combined with thiopental, was much less effective. That so many patients responded attests to the minimal anesthesia of the procedure; that so few remembered is not particularly comforting because it has been demonstrated that, in some cases, subconscious recall has long-lasting effects (18).

With respect to the mother's cardiovascular responses to intubation and surgery, the effects of the three induction techniques were comparable. Although heart rate remained lower in the ketamine group after induction, the clinical significance of this for healthy women is probably minor. Certainly the combination offered no advantage over either drug employed alone at a higher dosage.

Emergence phenomena such as dreams or hallucinations that are associated with ketamine are dose-related and brief (19). Some studies even suggest that dreams and hallucinations attributed to ketamine may instead be illusions produced by a fluctuating level of consciousness during a prolonged emergence after ketamine administration (20). When used in lower doses (<2 mg/kg) and in combination with other drugs (barbiturate, benzodiazepine, or N_2O among others), the incidence of these phenomena is low and similar to that observed with general anesthetic techniques without ketamine (21). In the present study, patients received a low dose of ketamine (1 mg/kg) followed

by 70% N_2O and, after delivery, fentanyl. Patients were anesthetized during the redistribution of ketamine and, by the time anesthesia was discontinued, circulating ketamine levels probably were low and emergence phenomena were minimal. All the induction techniques studied resulted in a low incidence of dreams (<20%) and all dreams were reported as pleasant. No patients exhibited postoperative dysphoria.

With respect to the newborn, no difference could be shown among scores of infants from the three groups. The blood gas values, Apgar scores, and neurobehavioral test results were all good and indistinguishable among groups.

Ketamine (1 mg/kg) induction for cesarean section markedly decreased intraoperative responsiveness with few side effects. The combination of ketamine and thiopental, both at low doses (0.5 mg/kg and 2 mg/kg, respectively), appears to offer little advantage over thiopental (4 mg/kg) with respect to intraoperative responsiveness, and was quite inferior to ketamine (1 mg/kg) alone.

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The Effects of Midazolam on Cerebral Blood Flow and Oxygen Consumption and Its Interaction with Nitrous Oxide

William E. Hoffman, PhD, David J. Miletich, PhD, and Ronald F. Albrecht, MD

The effects of the intravenous infusion of midazolam on cerebral blood flow (CBF) and cerebral oxygen consumption (CMRO₂) were measured in rats in the presence and absence of nitrous oxide. Midazolam produced 40–45% decreases in CBF with no difference in response between nitrous oxide and nitrogen-ventilated rats. CMRO₂ decreased 55% during midazolam infusion in rats ventilated with nitrogen,

significantly more (P < 0.05) than in rats ventilated with nitrous oxide (35%). We conclude that cerebrovascular responses to midazolam infusion were not altered by nitrous oxide and suggest that nitrous oxide may slightly but significantly stimulate brain metabolism during midazolam infusion.

Key Words: HYPNOTICS, BENZODIAZEPINES—midazolam. ANESTHETICS, GASES—nitrous oxide. BRAIN—blood flow, metabolism.

Nitrous oxide (N_2O) has been reported as having little effect on cerebral blood flow (CBF) or cerebral oxygen consumption (CMRO₂) in the rat (1,2). However, in other species and after certain anesthestic procedures, N_2O increases CBF and CMRO₂ (3,4). Although N_2O potentiates the action of other anesthetics, the effects of N_2O plus other anesthetics on CBF and CMRO₂ are controversial. Carlsson et al. (5) reported that in rats, diazepam given alone had no significant effect on brain oxygen consumption but that diazepam given with N_2O decreased both CBF and CMRO₂. In contrast, Nugent et al. (6) concluded that N_2O may stimulate brain metabolism in dogs and blunt the decrease in metabolism produced by other anesthetics. More recently, Sakabe et al. (7) found that N_2O significantly attenuates the decrease in brain glucose utilization produced by pentobarbital anesthesia. It was recently reported that midazolam given in combination with N_2O produced dose-related decreases in CBF and CMRO₂ in the rat (8). In the present studies, we have investigated the extent to which N_2O may modify the cerebral metabolic effects of midazolam.

Methods

Surgical Preparation

Six-month-old male Sprague–Dawley rats were anesthetized with halothane in a bell jar, tracheostomized, and ventilated with 1% halothane in O_2 using a Harvard small animal respirator. Body temperature was maintained at 37°C, and arterial blood Pco₂ was maintained between 35 and 40 torr by adjusting ventilation. Bilateral femoral cutdowns were performed, and both femoral arteries and both femoral veins were cannulated with Clay–Adams Intramedic polyethylene catheters filled with heparinized normal saline solution. These catheters were used for continuous monitoring of heart rate and pressure, as well as for blood withdrawal and drug administration. The left ventricle was catheterized via the right common carotid artery for microsphere injections. Pressure tracings were monitored to ensure proper catheter placement. A Hewlett–Packard pressure transducer and chart recorder was used in all cases. The skull was exposed, a small hole was drilled into the sagittal sinus, and a catheter was inserted for withdrawal of sagittal sinus blood samples.

After completion of surgery, halothane was discontinued, and 70% N_2O and 30% O_2 was administered for a 45-min equilibration period. Muscle relaxation was achieved with 1 mg/kg d-tubocurarine intravenously (IV).

Testing Procedures

At the end of the 45-min equilibration period, each rat received IV midazolam injections of either 0.02, 0.2, or 2 mg/kg, given according to a random schedule. This was followed by a 15-min infusion of 0.0025, 0.025, or 0.25 mg·kg^{-1}·min^{-1} for a total dose of 0.057, 0.575, or 5.75 mg/kg, respectively, in each rat, given over the 15-min infusion period. The volume infusion rate was 0.1 ml·kg^{-1}·min^{-1} in each rat, irrespective of midazolam dose. In half the animals, N_2 was substituted for N_2O in the inspired gases after the initial bolus injection of midazolam and at the start of the 15-min drug infusion. The rest of the animals were maintained with N_2O, O_2 inspiration during midazolam infusion. This was done to ensure that each rat was sedated with N_2O, midazolam, or both during the entire testing procedure. Microsphere tests were performed at the end of the 15-min midazolam infusion in both groups of rats. A final group of rats received only sham saline infusions and were ventilated with 70% N_2O, 30% O_2 during the infusion period.

Microspheres

Fifteen micron microspheres labeled with cobalt-57 (New England Nuclear) were used. Stock solutions containing 500,000 microsphere/ml were suspended in isotonic saline with 0.1% Tween-80. Ventricular pressure pulses were monitored before each injection of microspheres. Microspheres were vortexed for 1 min, after which 0.2 ml were withdrawn (100,000 microspheres), injected into the left ventricle via the ventricular catheter (dead space = 0.06 ml), and flushed with 0.2 ml saline. Starting immediately before each injection of microspheres and continuing for 45 sec after the end of each injection, blood was withdrawn from a femoral artery at a rate of 0.4 ml/min using a Harvard infusion-withdrawal pump. Arterial samples for measurement of blood gas tensions were obtained at the end of the microsphere injection. Arterial and sagittal sinus blood samples were also taken after injections of microspheres for measurement of cerebral arterial–venous O_2 content. Blood gas tensions and pH were measured with an IL 1303 blood gas analyzer, and oxygen content was measured using an IL 282 cooximeter. Mean arterial blood pressure was measured continuously throughout the injection of microspheres from the second femoral artery to ensure that blood pressure did not change appreciably. Blood pressure and heart rate records were taken at the end of the 15-min infusion period and before each microsphere injection. At the end of the microsphere injection, the rat was sacrificed, and the brain was removed and sectioned into left and right cortical and subcortical samples and weighed.

Microsphere radioactivity in brain and blood samples was measured using a Nuclear Chicago 1035 Gamma Counter and a Nuclear Data 600 multichannel analyzer, and CBF was measured according to the methods of Heymann et al. (9). $CMRO_2$ was calculated as the product of cortical CBF, corrected for brain weight, and cerebral arterial–venous blood O_2 content difference.

Drug and Reagents

Midazolam maleate (RO 21-3981/1, Hoffman–LaRoche, Inc., Nutley, NJ) was dissolved in normal saline to a stock concentration of 0.2 mg/ml. Microspheres were suspended in normal saline solution with Tween-80 0.01% to a concentration of 500,000 microspheres/ml.

Statistical Methods

All data are reported as mean ± SEM. Statistical evaluation included analyses of variance to compare the effects of midazolam in N_2O- and N_2-ventilated rats, and unpaired t-tests to compare intragroup differences using a Bonferroni correction.

Results

The hemodynamic effects of control nitrous oxide anesthesia and 15-min midazolam infusions, and the effects on blood gas tensions are shown in Table 1. Midazolam produced a non-dose-dependent 10–20% decrease in blood pressure in rats being ventilated with nitrogen or nitrous oxide, which was significant in both groups, as indicated by analysis of variance ($P < 0.05$). During midazolam infusion, heart rate in nitrogen-ventilated rats was elevated compared to that of rats receiving the control N_2O treatment ($P < 0.05$). Cerebral oxygen extraction, as indicated by arterial–sagittal sinus O_2 content (AVO_2), was consistently greater in rats ventilated with N_2O than it was in rats ventilated with N_2 during midazolam infusion. Arterial blood gas tensions remained unchanged because ventilation was controlled. Changes in CBF and $CMRO_2$ are shown in Figures 1 and 2. Dose-related decreases were produced in cortical and subcortical CBF during midazolam infusion. These changes were not significantly different in nitrogen- and nitrous oxide-ventilated rats. There was no significant difference in CBF between right and left cortical or subcortical tissues during midazolam treatment in nitrous oxide- or nitrogen-ventilated rats. The average right

Table 1. Effects of Midazolam on Cerebral Hemodynamics and Blood Gas Tensions in Rats Ventilated with N_2O and N_2

Midazolam dose (mg/kg)	n	Blood pressure (mm Hg)	Heart rate (beats/min)	Pa_{CO_2} (mm Hg)	Pa_{O_2} (mm Hg)	pH	AVO_2 (ml O_2/100 ml)
Control (70% N_2O)							
none	12	132 ± 3	356 ± 16	36.9 ± 0.7	143 ± 11	7.40 ± 0.01	6.1 ± 0.1
Nitrous oxide-ventilated rats							
0.057	11	112 ± 7[a]	381 ± 10	35.8 ± 0.8	141 ± 13	7.39 ± 0.01	6.4 ± 0.4
0.575	13	114 ± 9	387 ± 16	37.2 ± 0.5	138 ± 11	7.41 ± 0.01	6.5 ± 0.3
5.750	10	108 ± 8[a]	392 ± 8	36.2 ± 1.4	132 ± 7	7.41 ± 0.02	6.8 ± 0.3[a]
Nitrogen-ventilated rats							
0.057	7	114 ± 6[a]	442 ± 13[a]	36.8 ± 0.6	141 ± 2	7.42 ± 0.02	5.0 ± 0.4[a]
0.575	11	117 ± 3[a]	426 ± 15[a]	36.5 ± 0.3	149 ± 8	7.42 ± 0.02	4.8 ± 0.2[a,b]
5.750	6	123 ± 5	393 ± 15	36.0 ± 0.5	126 ± 5	7.44 ± 0.02	5.0 ± 0.2[a,b]

Data presented as mean ± SE.
[a] $P < 0.05$ control N_2O vs midazolam infusion at each dose.
[b] $P < 0.05$ N_2O vs N_2 ventilation at each midazolam dose.

vs left cortical CBF in N_2O- and N_2-ventilated rats at each midazolam dose were as follows: control N_2O, right = 168 ± 15 ml·100g^{-1}·min^{-1}, left = 172 ± 10 ml·100g^{-1}· min^{-1}; 0.057 mg/kg midazolam, right = 130 ± 8 ml·100g^{-1}·min^{-1}, left = 146 ± 12 ml·100g^{-1}·min^{-}; 0.575 mg/kg midazolam, right = 107 ± 10 ml·100g^{-1}·min^{-1}, left = 108 ± 7 ml·100g^{-1}·min^{-1}; 5.75 mg/kg midazolam, right = 99 ± 11 ml·100g^{-1}·min^{-1}, left = 93 ± 7 ml·100g^{-1}·min^{-1}. Subcortical blood flow showed a similar lack of difference between right and left hemispheres at each test dose. Cortical $CMRO_2$ showed dose-related decreases during midazolam infusion. $CMRO_2$ was consistently lower in rats ventilated with nitrogen than in rats ventilated with nitrous oxide at each midazolam dose, and this difference in response was statistically significant ($P < 0.05$).
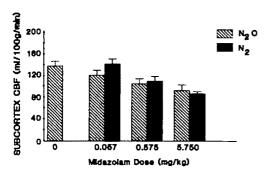
Discussion

These data show that intravenous infusion of midazolam produces modest cardiovascular depression and dose-related decreases in CBF and $CMRO_2$. Decreases in CBF induced by midazolam were similar in rats ventilated with either nitrous oxide or nitrogen in oxygen. In contrast, rats ventilated with nitrous oxide showed significantly less decrease in $CMRO_2$ during midazolam infusion than did rats ventilated with nitrogen. These results suggest that nitrous oxide produces a small but significant stimulation of brain metabolism in the presence of midazolam. This is consistent with other reports that suggest that nitrous oxide may attenuate the cerebral depressant effects of anesthetics while potentiating anesthesia (3,4,6,7). It is inconsistent, however, with studies suggesting that benzodiazepines produce cerebral metabolic depression only in the presence of nitrous oxide (5).

Several reports indicate that benzodiazepines produce decreases in CBF and $CMRO_2$. Rockoff et al. (10) found that 4 mg/kg lorazepam induced light sleep in monkeys and decreased $CMRO_2$ by 21–30%. In dogs, Maekawa et al. (11) reported that 0.25 mg/kg diazepam produced a transient decrease in $CMRO_2$. Also in dogs, Sari et al. (12) found that 0.25 mg/kg diazepam produced a moderate but statistically significant depression in brain metabolism. There is controversy, however, concerning how nitrous oxide may affect their responses. Carlsson et al. (5) reported that diazepam (0.75 and 7.5 mg/kg) decreased CBF and $CMRO_2$ approximately 40% only in the presence of nitrous oxide ventilation. When nitrogen was substituted for nitrous oxide, diazepam produced no change from control values in $CMRO_2$. They suggested that because nitrous oxide has little effect on brain oxygen consumption when given alone, its effect when combined with diazepam was due to a central interaction between the two agents which could not be shown separately. Their results did not agree with the conclusions of Nugent et al. (6) that nitrous oxide ventilation may have the opposite effect. Nugent et al. found that diazepam and midazolam injections produced dose-dependent decreases in CBF and $CMRO_2$ in dogs given nitrous oxide. However, in contrast to the results of Carlsson et al. (5), no significant difference in $CMRO_2$ was seen between animals given diazepam with or without nitrous oxide ventilation. Nugent et al. (6) found no large differences in $CMRO_2$ in animals given diazepam or midazolam with or without N_2O. They suggested that N_2O, which moderately stimulates $CMRO_2$ in their model, may actually blunt drug-induced decreases in $CMRO_2$. This is consistent with the results of Sakabe et al. (13), who showed that cerebral glucose utilization was decreased by pentobarbital anesthesia but that these decreases were attenuated when N_2O was combined
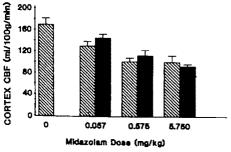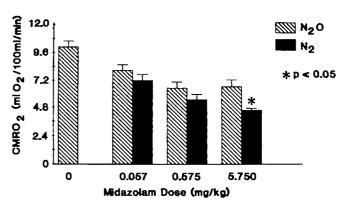
Figure 1. Subcortical (upper graph) and cortical (lower graph) CBF produced by a 15-min intravenous infusion of midazolam, at three different total doses. Control data presented as zero-dose midazolam in rats ventilated with N_2O-O_2. Analyses of variance indicate that midazolam produced statistically significant decreases in cortical and subcortical CBF in both N_2O- and N_2-ventilated rats ($P < 0.05$), with no significant difference between the two groups ($P > 0.10$). The number of rats tested in each group is shown in Table 1.

Figure 2. Cortical $CMRO_2$ after midazolam infusion in rats ventilated with nitrous oxide or nitrogen. Analyses of variance showed a statistically significant decrease in $CMRO_2$ in both N_2O- and N_2-ventilated animals ($P < 0.05$), with the decrease significantly greater in N_2-ventilated rats than in rats ventilated with N_2O ($P < 0.05$). The significant value shown in this figure indicates a difference between N_2O- and N_2-ventilated rats at 5.75 mg/kg midazolam, as indicated by the Bonferroni test.

with pentobarbital. Inhibition of anesthetic-induced cerebral metabolic depression by N_2O would also agree with data presented here. We found that midazolam decreased CBF and $CMRO_2$ in rats ventilated with and without nitrous oxide with a small but significant stimulation in $CMRO_2$ produced by N_2O compared to nitrogen ventilation. Our results do not support the suggestion that N_2O potentiates the cerebral depressant effects of benzodiazepines, but suggest that N_2O may have a modest stimulatory effect when combined with other anesthetics (3,4,6).

Some consideration should be given to the methods used here. First, there is a possibility that catheterization of the right carotid artery for microsphere injections may have altered CBF by limiting blood flow to the right cerebral hemisphere. This was suggested by Seyde and Longnecker (14) when they found that CBF to the cerebral hemisphere ipsilateral to carotid ligation may be limited during high doses of inhalation anesthesia, which produce cerebrovasodilation. This is consistent with a report from this laboratory that differences in right versus left hemisphere CBF may be significant during cerebrovasodilation induced by hypoxia or hypercapnia (15). In this study, however, CBF seen in the right and left

cerebral hemisphere were not significantly different during N_2O anesthesia from those during midazolam treatment. This is probably an indication of the ability of the brain to maintain perfusion of both hemispheres when cerebrovascular resistance is normal or elevated. CBF to the cerebral hemisphere ipsilateral to carotid ligation may be compromised, however, under conditions in which cerebrovasodilation is significant.

Another consideration is that nitrous oxide anesthesia with paralyzation may not produce a state relating to normal unanesthestized rats but instead a heightened sympathetic state. This possibility is suggested by the report of Seyde and Longnecker (14), who found that total brain CBF was 90 ± 5 ml · $100g^{-1}$ · min^{-1} in an unanesthetized state. However, other studies have shown that CBF and brain metabolism are similar in unanesthetized and in paralyzed N_2O-ventilated rats (2,16). In fact, the cortical CBF values reported by Dahlgren et al. (2) under unanesthetized and N_2O-ventilated conditions are similar to those seen here under control conditions. Although the question of CBF and $CMRO_2$ under a true control state for unanesthetized rats remains controversial, results presented here indicate that cerebrovascular and cerebral metabolic responses to midazolam are similar during nitrous oxide and nitrogen ventilation.

Nitrous oxide is a valuable anesthetic for both clinical and experimental purposes. Clinically, N_2O can be combined with other anesthetic agents to decrease the amount of anesthetic required to produce surgical anesthesia (14). Experimentally, the ability of N_2O to produce analgesia with little or no cardiovascular or

cerebral metabolic depression makes it a useful agent for control measurements in the rat (1,2). The present study supports the suggestion of Nugent et al. (6) that N_2O may actually attenuate the cerebral metabolic depression produced by sedative and anesthetic agents. Though the cerebral metabolic depression produced by midazolam was significantly attenuated by nitrous oxide versus nitrogen ventilation in these studies, these effects were modest, and the dose-related effects of midazolam on CBF and $CMRO_2$ were apparent with inhalation of either gas.

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Transperitoneal Oxygenation with Fluorocarbons

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KLEIN J, FAITHFULL NS, SALT PJ, TROUWBORST A. Transperitoneal oxygenation with fluorocarbons. Anesth Analg 1986;65:734-8.

This work investigated the improvement of arterial oxygenation in hypoxic rats during peritoneal perfusion with the oxygen-carrying perfluorocarbon blood substitute FC_{43}. Three groups of six Wistar rats were ventilated with hypoxic gas mixtures to obtain an arterial oxygen tension (PaO_2) of approximately 55 mm Hg. Two groups were subjected to peritoneal perfusion at 20 ml/min with oxygenated FC_{43} or the gelatine solution Haemaccel. A third group was sham operated but not perfused. In both perfused groups PaO_2 increased significantly, more so in the FC_{43} group. Carbon dioxide tensions significantly decreased only in the FC_{43} group. Significant increases in arterial oxyhemoglobin saturation were seen after 15 min in the FC_{43} group and after 60 min in the Haemaccel group. More than 15% of oxygen consumption could be delivered by peritoneal perfusion with FC_{43}.

Key Words: PHARMACOLOGY—fluorocarbons.

Various methods of whole body oxygenation without the use of the lungs have been investigated experimentally. Some, such as the intravenous injection of oxygen (1) and the use of extracorporeal oxygenators (2), have been employed clinically, but have not proved very satisfactory.

The use of the peritoneum as a gas exchanger has been investigated and moderate increases in the PaO_2 and hemoglobin saturation (SaO_2) have been achieved in rabbits and cats by the intraperitoneal installation of hydrogen peroxide (3). However, this method resulted in gas embolization of the pulmonary and coronary arterial beds when higher concentrations of the solution were used. Slight increases in PaO_2, but no appreciable carbon dioxide clearance, were also achieved after direct injection of oxygen into the peritoneal cavity of dogs (4).

Fluorocarbons are inert chemicals that have a very high solubility for respiratory gases, and PaO_2 was increased and $PaCO_2$ decreased in hypoxic rabbits subjected to peritoneal perfusion (PP) with emulsions of these substances (5). Further work in rats reconfirmed oxygenation possibilities and demonstrated that the $PaCO_2$ could be reduced by PP with both fluorocarbons and the gelatine solution Haemaccel (6). In the latter work the animals were not ventilated and a certain amount of cardiorespiratory embarrassment was probably caused by the presence of intraperitoneal fluid. Before proceeding to more comprehensive studies using a respiratory distress model, it is important to ascertain if increases in the PaO_2 after PP with fluorocarbon emulsions are in fact more than those produced by simple solutions. Our work was designed to that end.

Methods

Three groups of six Wistar rats (body weight 400–450 g) were anesthetized with nitrous oxide, oxygen, and halothane. After endotracheal intubation, they were ventilated with 0.5% halothane vaporized in nitrous oxide and oxygen (2:1) using a Rosche Baby Kontrol ventilator adjusted to maintain end-expired carbon dioxide concentration at 4.5–5%, which was continuously monitored using a Gould Godart Mark III capnograph. Muscular relaxation was provided by a continuous intramuscular infusion of pancuronium bromide (0.3 mg·kg^{-1}·hr^{-1}) delivered from a Braun Melsungen Perfusor apparatus.

The right femoral artery was cannulated and a catheter was passed from the left femoral vein into the right atrium. Catheters were connected to Statham P23Dc transducers and pressures were recorded using a Grass 7D polygraph. The intraabdominal pressure was similarly monitored by means of a 1 mm internal diameter catheter inserted into the upper abdomen

Table 1. Composition of FC_{43} and Haemaccel

FC_{43}		Haemaccel	
Perfluorotributylamine	20.0	Polygeline	3.5
Pluronic F68	2.5		
NaCl	0.6	Na^+	0.33
KCl	0.34	K^+	0.0198
$MgCl_2$	0.02	Ca^{2+}	0.025
$CaCl_2$	0.028	Cl^-	0.5
$NaHCO_3$	0.210		
Glucose	0.180		
Hydroxyethyl-starch	3.0		
pH	7.4–7.6	pH	7.3

Figures are in weight/vol%.

in those animals in which peritoneal perfusion was performed. The electrocardiogram was recorded from lead II.

Arterial blood gas and acid–base status were measured using a Radiometer ABL1 Acid–base Laboratory; the hemoglobin concentration and oxyhemoglobin saturation were measured with a Radiometer OSM2 Hemoximeter. Rectal and esophageal temperatures were monitored using an Elab instruments multitemperature monitoring device type 7F5, and a thermostatically controlled heating blanket was used to maintain body temperature between 37 and 38°C.

A 7 French gauge Argyle oxygen catheter was inserted through a small incision in the left lower abdominal quadrant and advanced into the left paracolic gutter. This catheter served for the inflow of the perfusate, which was removed from the abdominal cavity through a 16-gauge Salem sump drain inserted through a small incision in the right lower abdominal quadrant and placed in the right paracolic gutter.

After the surgical preparation was complete, blood gas and oxygenation parameters were measured while the rats were ventilated with a 2:1 oxygen and nitrous oxide mixture. These measurements were repeated at 10 and 20 min to ensure stability of the preparation. Inspired oxygen concentration was then gradually lowered until the arterial PO_2 dropped to the region of 50 mm Hg. After reaching this point, two other sets of measurements were taken at 10 min intervals. After the third measurement, PP was commenced in two groups of animals; Haemaccel was employed in one group, and in the other group perfusion was with FC_{43}. The compositions of the two perfusion fluids are shown in Table 1. A third group of animals was sham operated and, although abdominal catheters were inserted, no PP was carried out.

The perfusates were oxygenated using a homemade bubble oxygenator through which 100% oxygen was passed; blood gas and acid–base status was as-

sessed at 15 min intervals. The mean PO_2 of the FC_{43} was 497.1 (± 8.60 SEM) mm Hg and that of the Haemaccel was 453.2 (± 12.9 SEM) mm Hg, while pH was 8.50 (± 0.13 SEM) and 7.20 (± 0.03 SEM), respectively. The perfusates were warmed to 37°C by passage through a thermolyne DR1 heating bath, circulated at a rate of 20 ml/min using a roller pump, and drained from the peritoneal cavity by gravity. During perfusion, arterial blood gas and oxygenation parameters were measured every 15 min over a period of 1 hr.

At the end of the experiments, arterial blood was taken and centrifuged for 15 min in a Christ hematological centrifuge to ascertain whether detectable quantities of fluorocarbons had entered the circulation. On no occasion was a measurable fluorocrit obtained.

Statistical analysis of the results was performed using paired or unpaired Student's t-tests where appropriate. Statistical significance was accepted at a P value of less than 0.05.

Results
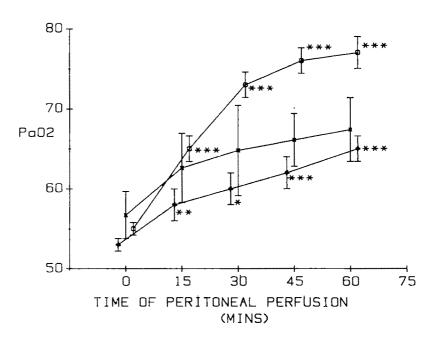
The general condition of the animals in all groups remained good throughout the experimental period. The induction of hypoxia caused statistically significant decreases in arterial blood pressure and increases in heart rate. There were no significant changes in these parameters or in central venous pressures during the perfusion period. Peritoneal perfusion caused no significant alterations in intraabdominal pressure, and at no time was pressure raised more than 2.5 mm Hg above preinfusion baseline pressures.

The changes observed in the PaO_2 during peritoneal perfusion with Haemaccel and FC_{43} are shown in Figure 1 together with the PaO_2 of the sham-operated, nonperfused control group. As can be seen, PaO_2 values were significantly higher than the hypoxic control values at all times during peritoneal perfusion with FC_{43} and Haemaccel. At all times the increases in PaO_2 in the FC_{43} group were significantly greater than those in the Haemaccel group. No significant changes were seen in the PaO_2 of the control group.

The above changes in the PaO_2 were represented by increases in saturation of the arterial blood (Fig. 2). At all time during perfusion the SaO_2 was significantly raised in the FC_{43} group in comparison with the preperfusion values. On the other hand, in the Haemaccel group the increases reached significance only after 60 min of perfusion. Saturations in the FC_{43} group were significantly higher than those in the Haemaccel group at all times during perfusion.

Carbon dioxide partial pressure in the arterial blood

Figure 1. Arterial PaO$_2$ in mm Hg before and during peritoneal perfusion in the FC$_{43}$ group (represented by open circles) and the Haemaccel group (plus signs). The nonperfused control group is signified by multiplication signs (×). Significant differences from the preperfusion values are indicated by asterisks. *$P < 0.05$; ** $P < 0.01$; ***$P < 0.001$.

Figure 2. Arterial SaO$_2$ (in percent) before and during peritoneal perfusion in the FC$_{43}$ group (represented by open circles) and the Haemaccel group (plus signs). The nonperfused control group is signified by multiplication signs (×). Significant differences from the preperfusion values are indicated by asterisks. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

was significantly lowered only in the FC$_{43}$ group. This was seen at 30 and 60 min of perfusion (Fig. 3). No significant decreases were seen in the other two groups. There were no significant changes in the pH of the arterial blood in any of the three groups.

Discussion

The two perfusion fluids employed in these experiments both have similar osmotic pressures; the value for FC$_{43}$ is 290–300 mosm/L (7) and that for Haemaccel is 301 mosm/L (8). The dynamic viscosity of FC$_{43}$ is

2.4 cp at 35°C (7) and is somewhat higher than that of Haemaccel at 1.15–1.2 cp (8). The lower viscosity of the latter might imply that Haemaccel would be better distributed throughout the peritoneal cavity and that the efficiency of available gas exchange would be greater than would be the case with FC$_{43}$.

The in vitro pH values are similar—7.4 for Haemaccel (8) and 7.4–7.6 for FC$_{43}$ (7). It is thus not entirely clear why the pH of the FC$_{43}$ was so much higher than these values when measured during the present PP experiments. Interestingly, a similar rise in pH of the fluorocarbon perfusate (Fluosol-DA 20%) was seen
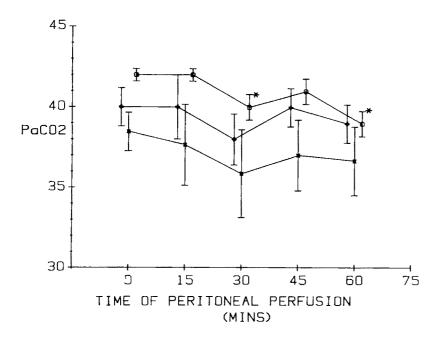
Figure 3. Arterial PaCO₂ in mm Hg before and during peritoneal perfusion in the FC₄₃ group (represented by open circles) and the Haemaccel group (plus signs). The nonperfused control group is signified by multiplication signs ($\times$). Significant differences from the preperfusion values are indicated by asterisks. $^*P < 0.05$.

when rabbits were subjected to PP (5). On both occasions the perfusates were oxygenated using 100% oxygen and it may be that the addition of 5% CO_2 is necessary to produce a normal pH: the pH of Fluosol-DA has been reported to adjust to 7.40 when the product is equilibrated with 95% O_2 and 5% CO_2 (9). This increase of pH of fluorocarbon emulsions may be an advantage as it has been shown that increasing the pH in the portal circulation causes an increase in portal blood flow (10), which might lead to a greater uptake of oxygen.

The most striking difference between the two perfusates is in their solubility for oxygen: FC_{43} dissolves 0.82 ml $O_2 \cdot 100$ ml emulsion$^{-1} \cdot 100$ mm Hg^{-1} (7) whereas Haemaccel only takes up 0.28 ml under the same conditions (11). The amount of oxygen available for uptake into the portal circulation depends on the difference between the PO_2 of the perfusate and the PO_2 of the peritoneal cavity. The latter value is not known to us but is probably around 42 mm, which was the measurement found in the rabbit under normoxic conditions (12). Thus under normoxic conditions, with a perfusion rate of 20 ml/min and a mean PO_2 of the FC_{43} of 497.1 mm Hg, it can be calculated that FC_{43} could deliver a maximum of 0.75 ml O_2/min. Under hypoxia, intraperitoneal PO_2 will be at a lower value, and hence slightly more oxygen can be released from FC_{43}.

At the end of 1 hr of peritoneal perfusion with FC_{43}, the mean arterial saturation had risen by 5.63%. The mean cardiac output of a Wistar rat is 203 ml·kg^{-1}·min^{-1} (13) and hence a 412 g rat (the mean weight of the animals in the FC_{43} group) would have an output of

83.6 ml/min. The mean hemoglobin concentration of the rats in the FC_{43} group was 12.3 g/100 ml, and it can be calculated that in order to effect the above change in arterial hemoglobin saturation we would need an additional oxygen supply of: $(0.123 \cdot 83.6 \cdot 0.0563) \cdot 1.34 = 0.78$ ml O_2/min. This figure is consistent with the 0.75 ml of oxygen available from the FC_{43}, which was calculated above.

The peritoneum is highly vascular and forms one of the largest absorptive surfaces in the body (14); it has been shown that substances administered intraperitoneally are primarily absorbed into the portal circulation (15). Approximately 18.5% of the cardiac output (or 37.15 ml of blood) passes through the portal vein of a rat per minute (16). The saturation of the portal blood of a rat is not known to us, but based on the assumed normoxic intraperitoneal PO_2, it will be in the range of 75%. The maximum additional amount of oxygen that can be transported by the portal vein is: $(0.25 \cdot 12.3 \cdot 1.34) \cdot 0.3715 = 1.53$ ml O_2. The hemoglobin saturation in the portal vein is almost certainly lower than 75% during hypoxia; thus the calculated figure is almost certainly too low. Nevertheless, the above figure indicates that the amount of oxygen that was calculated above as provided by peritoneal perfusion could easily be delivered.

The above calculations make a number of basic assumptions. Nevertheless, they do demonstrate that the amount of oxygen provided by PP with FC_{43} was possible both from the point of view of the amount of oxygen present in the FC_{43} and from the oxygen transport capacity through the portal vein.

The carbon dioxide solubility of FC_{43} at body temp-

perature is approximately 9 ml·100 ml^{-1}·100 mm Hg^{-1} (7). Under similar conditions 6 ml of carbon dioxide can be dissolved in aqueous media (17). This difference suggests that PP with FC$_{43}$ would decrease PaCO$_2$ levels more than when Haemaccel was employed, a conclusion our experiments confirmed.

The oxygen consumption of a 412 g rat is 5.06 ml/min (18); peritoneal perfusion with FC$_{43}$ provided 15.4% of this amount. More oxygen might possibly be absorbed by this route, especially under conditions of raised cardiac output. However, increased cardiac output would necessitate increased flows of perfusate or the employment of higher concentrations of fluorocarbons in the emulsion—it might even be possible to use fluorocarbons as perfusate and thus, for the same perfusion rate, vastly increase the oxygen supplied.

In conclusion, this study has demonstrated that some degree of oxygenation can be obtained by peritoneal perfusion with Haemaccel. However, the use of FC$_{43}$ as perfusate resulted in a greater exchange of both oxygen and carbon dioxide, and FC$_{43}$ was able to provide a small but significant bulk movement of oxygen across the peritoneal membrane.

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Prospective Evaluation of Risk of Protamine Reactions in Patients with NPH Insulin-Dependent Diabetes

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LEVY JH, ZAIDAN JR, FARAJ B. Prospective evaluation of risk of protamine reactions in patients with NPH insulin-dependent diabetes. Anesth Analg 1986;65:739–42.

Patients with NPH (neutral protamine Hagedorn) insulin-dependent diabetes may have an increased risk for protamine reactions because of prior sensitization. During one year, we prospectively evaluated 50 at-risk cardiac surgery patients for clinical reactions and determined in vitro histamine release when protamine was added to a preoperative blood sample. We speculated that in vitro histamine release would predict a reaction to protamine given clinically for neutralization of heparin. Twenty-five patients randomly received prophylactic corticosteroid and/or antihistamine

pretreatment for allergic reactions. The incidence of clinical reactions to protamine was 1/50 (2%) in NPH insulin-dependent diabetic patients (1/25 in pretreated patients vs 0/25 in patients not receiving pretreatment). One pretreated NPH diabetic patient released histamine in vitro but did not demonstrate clinical signs of a reaction following protamine administration. One other NPH diabetic patient pretreated with corticosteroids developed severe pulmonary hypertension despite the absence of in vitro histamine release. Therefore, in vitro histamine release does not predict protamine reactions.

Key Words: BLOOD, COAGULATION—protamine. AL-LERGY—protamine. ANESTHESIA—cardiovascular.

Protamine, a protein isolated from fish sperm, is the only clinically available drug that reverses the anticoagulant activity of heparin. The reported spectrum of protamine reactions ranges from mild vasodilatation and myocardial depression to life-threatening pulmonary and systemic vascular changes (1,2). Because patients with neutral protamine Hagedorn (NPH) or protamine zinc insulin-dependent diabetes may be sensitized to protamine, investigators have suggested that these patients have an increased risk of protamine-related anaphylactic reactions (3–6). By indicating which patients should not receive protamine (7), preoperative identification could help provide them with better clinical care. Retrospective analysis of patients following suspected anaphylactic reactions to protamine demonstrated in vitro leukocyte histamine release (4). Therefore, we followed these patients for clinical reactions and prospectively evaluated whole blood histamine release in vitro as a predictive test for in vivo clinical reactions (8).

Methods

After Human Investigation Committee approval, between March 1, 1984 and March 1, 1985 blood samples were drawn before elective cardiac surgical procedures from fifty patients taking NPH insulin. Arterial blood obtained 30–60 min prior to induction of anesthesia was placed in tubes containing sodium heparin, immediately placed on ice and studied within 4 hr. Preoperatively patients received their calcium channel blocking, adrenergic β-receptor blocking, and nitrate medications, and were sedated with morphine, scopolamine, and diazepam. Pulmonary arterial and radial arterial catheters were inserted prior to anesthetic induction. Pretreatment with antihistamines and/or corticosteroids followed anesthetic induction in 25 of 50 patients, depending on the anesthesiologist. No attempt was made to alter the clinical practice of the attending anesthesiologist. Table 1 lists the drugs given to the pretreated patients. Following cardiopulmonary bypass, heparin activity was neutralized with protamine, 3–4 mg/kg, infused over 5–30 min. Clinical reactions were defined as acute bronchospasm, noncardiogenic pulmonary edema, pulmonary hypertension, or decreases in mean arterial pressure within 20 min after protamine administration. Hypotension had to be unrelated to changes in heart rate or rhythm, to surgical manipulation, hy-

Table 1. Drugs Used for Pretreatment

Number of patients	Drugs
14	Methylprednisolone, 2 g; Diphenhydramine, 50–100 mg; Cimetidine, 300 mg
7	Methylprednisolone, 2 g
2	Dexamethasone, 20 mg; Diphenhydramine, 50–100 mg; Cimetidine, 300 mg
2	Diphenhydramine, 50–100 mg; Cimetidine, 300 mg

Table 2. Surgical Procedures

Number of patients	Procedure
39	Coronary artery bypass
6	Redo coronary artery bypass
2	Aortic valve replacement
2	Mitral valve replacement
1	Redo mitral valve replacement

povolemia due to bleeding, myocardial ischemia, overdosage of vasodilators, hypercarbia, or hypoxia.

In Vitro Allergy Testing

Protamine-mediated histamine release from whole blood was assessed by adding 0.01, 0.05, 0.2, 0.5, and 1.0 mg of protamine (Lilly) to plastic tubes containing 0.5 ml of Tris–albumin buffer and 0.5 ml of the patient's heparinized blood. Control tubes for baseline histamine release were prepared by mixing the buffer solution with blood. After a 15 min incubation in a 37° shaking water bath the tubes were centrifugated at 500 x g for 10 min. The plasma was separated and stored at minus 30°C until analyzed. A single isotopic radioenzymatic assay was used for the measurement of histamine based on the incubation of test samples and histamine controls in the presence of histamine-N-methyl-transferase from rat kidney and [^3H-methyl]-S-adenosyl-L-methionine in phosphate buffer, 0.05 mol/L, pH 7.9, at 37°C for 60 min (8). Interassay and intraassay coefficients of variation for the histamine assay are 5% and 7% respectively, with a sensitivity of 0.1 ng. Total blood histamine was determined by diluting 0.5 ml of whole blood with 1.5 ml of buffer and heating in a boiling water bath for 20 min. After centrifugation the supernatant was removed and stored at −30°C until analyzed.

The percentage of histamine release from 1.0 ml of blood by protamine was determined from the following formula: $100 \times A/B$ = percent histamine release, where A is the concentration of histamine in plasma after the incubation of whole blood with protamine minus the concentration of histamine in plasma after incubation with buffer alone, and B is the total concentration of histamine obtained in boiled blood.

Results

During the 12-month period, 1551 patients required cardiac surgery. Of the 1551 patients, 50 patients (3.2%) had NPH insulin-dependent diabetes. The surgical procedures are listed in Table 2. The total histamine content of the blood samples drawn was 150 ± 53 ng/ml ($\overline{X}$ ± SD). One of the pretreated diabetic patients demonstrated in vitro histamine release (Table 3), but administration of protamine to this patient after cardiopulmonary bypass did not produce cardiopulmonary changes. One other pretreated NPH diabetic patient undergoing coronary artery surgery who did not release histamine in vitro developed systemic hypotension and pulmonary hypertension within 10 min after protamine administration (Fig. 1). Initially this patient received epinephrine for resuscitation, but required isoproterenol, intraoperatively and postoperatively for persistent pulmonary hypertension after the reaction. The incidence of clinical reactions to protamine in non-NPH insulin-dependent diabetics was one in 1501 patients during the study period.

Discussion

Protamine-mediated leukocyte histamine release was chosen as the allergy test because retrospective evaluation of anaphylactic protamine reactions demonstrated in vitro histamine relase from leukocytes (4). Leukocyte-mediated histamine release, a standard technique of in vitro allergy studies that evaluates immunospecific immunoglobulin E (IgE) antibodies, requires 40–50 ml of blood and tedious separation procedures to isolate leukocytes (9). We used whole blood in an attempt to simulate in vivo conditions. An enzymatic isotopic histamine assay, a test that accurately determines histamine concentration in whole blood, facilitated the development of a clinically useful test (8). Evaluation of this test in a diversified population of atopic patients revealed an excellent correlation between release of histamine in blood and intradermal antigen administration (8). The test is very sensitive; control nonallergic patients with negative skin tests did not release histamine from blood (8). Our study represents the first attempt to prospectively evaluate patients considered at risk for protamine reactions.

Patients receiving protamine-insulin preparations

Table 3. Percent In Vitro Whole Blood Histamine Release in Response to Protamine

	Protamine added (mg)				
	0.01	0.05	0.2	0.5	1.0
NPH diabetics					
In vitro histamine releasers (n = 1)	7.6	11.2	17.4	11	ns
Nonreleasers* (n = 49)	0.07 ± 0.2	0.09 ± 0.27	0.04 ± 0.2	0.05 ± 0.2	0.07 ± 0.25

The total histamine content for the blood samples was 150 ± 53 ng/ml.
*Data are expressed as $\bar{X}$ ± SD.
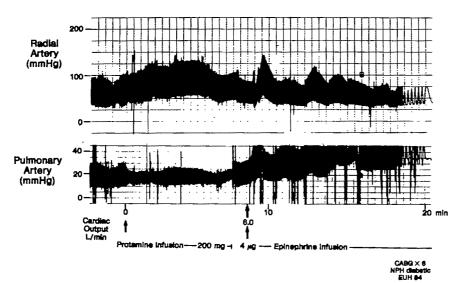
Figure 1. Hypotension and pulmonary hypertension after protamine administration in an NPH diabetic. Cardiac output obtained during the initial hypotensive episode was 6.0 L/min, and there were no ST–T wave changes indicative of myocardial ischemia. Epinephrine was subsequently administered as a 4 µg bolus followed by a variable rate of infusion to restore hemodynamic stability. Pulmonary capillary wedge pressure measurements were 8–14 mm Hg during the increases in pulmonary artery pressure. Isoproterenol was subsequently infused for persistent pulmonary hypertension.

have been reported to have a 27% incidence (4/15) of anaphylactic reactions to protamine used for heparin reversal after cardiac catheterization (3). Sharath et al. reported a 53% incidence (10/19) of protamine-specific IgE in insulin-dependent diabetic patients (6). Based on these reports, this group of individuals represents a significant risk for clinical reactions. The whole blood leukocyte histamine release assay represents an in vitro anaphylactic challenge, with histamine release a nonspecific marker to evaluate immunospecific antibodies to protamine.

One NPH diabetic patient released histamine in vitro but did not manifest cardiopulmonary changes following protamine administration; he had been pretreated with antihistamines intraoperatively. We therefore cannot exclude the possibility of in vivo histamine release in this patient, because prior administration of both H_1 and H_2 receptor antagonists may have prevented clinical manifestations. It is unclear why histamine release should occur in vitro without clinical signs of a reaction in vivo. The inability to correlate in vitro histamine release with clinical reactions suggests several possibilities: false-positive histamine release may occur, histamine may not be the major mediator of protamine reactions, or the

presence of protamine antibodies may not be predictive for clinical reactions. Although 53% of protamine-insulin-dependent diabetics are reported to have protamine-specific IgE antibodies, our incidence based on indirect evidence using whole blood leukocyte histamine was only 2% (1/50).

Another NPH diabetic patient did not release histamine in vitro but developed hypotension and pulmonary hypertension following protamine administration. Although epinephrine may have contributed initially to the increased pulmonary artery pressure, pulmonary vasoconstriction was sustained despite later isoproterenol administration. Although pulmonary vasoconstriction in one patient may be coincidental, this reaction may also represent an IgG-mediated reaction involving complement activation independent of leukocyte histamine release. Lakin et al. demonstrated that protamine anaphylaxis is mediated by an IgG complement-dependent antibody (10). Furthermore, classical complement activation has been demonstrated after an anaphylactic reaction to protamine, suggesting the presence of complement-mediated protamine effects that are independent of IgE (11). Complement activation liberates the anaphylatoxins, C3a and C5a (12,13). Leukocytes and platelets possess

cell membrane receptors that bind C5a to produce aggregation, microvascular occlusion, and synthesis of arachidonic acid metabolites (12,13). Thromboxane generated in this manner may be reponsible for the pulmonary hypertension observed in our patient (14).

Although methylprednisolone inhibits complement-induced granulocyte aggregation in vitro at doses of approximately 30 mg/kg, pretreatment with 2.0 g administered 2 hr before the protamine infusion did not prevent pulmonary hypertension (13). No data supports the use of corticosteroids as pretreatment for anaphylactic reactions. The use of antihistamines and corticosteroids for pretreating radiocontrast media reactions is well-established, but these reactions are anaphylactoid, representing nonimmunologic events (15). Life-threatening protamine reactions may represent anaphylaxis, true immunologic reactions mediated by antibodies. In these circumstances, the inability of large methylprednisolone doses to prevent anaphylactic reactions is more understandable.

Our prospective data suggest a lower incidence of clinical reactions to protamine in NPH insulin-dependent diabetic patients (2%, 1/50) compared to the retrospective analysis by Stewart et al., who suggested a 27% (4/15) incidence (3). The incidence of clinical reactions was not different with or without pretreatment (1/25 vs 0/25). It is unclear why such variation exists, but we used strict diagnostic criteria when prospectively evaluating patients. Although a variety of case reports and retrospective analyses implicate an association between NPH insulin use and protamine reactions, our in vivo and in vitro data both demonstrate a low incidence of allergy and reactions. The low incidence of protamine reactions after previous exposure may be explained by the fact that protamine is poorly antigenic and does not produce an allergic response in animals even with administration of Freund's adjuvant (16). In fact, most NPH insulin allergies are produced by insulin and not protamine (17). Previous reports of a 53% incidence of IgE antibodies in NPH insulin-dependent diabetics may represent false-positive results, because Sharath et al. evaluated IgE antibodies by means of a newly developed enzyme-linked immunosorbent assay test for protamine (6).

In summary, prospective evaluation suggested only a 1/50 (2%) incidence of clinical reactions to protamine in NPH insulin-dependent diabetics. Pretreatment for potential allergic reactions may have attenuated physiologic responses to histamine. Corticosteroidal pretreatment alone did not prevent pulmonary hypertension, therefore routine pretreatment may not be effective in all cases. In vitro whole blood histamine release to protamine was not a predictor for clinical reactions. Prospective evaluation for both protamine-specific IgE and complement-fixing IgG antibodies may more accurately predict protamine reactions.

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Pharmacokinetics and Pharmacodynamics of Atracurium during Isoflurane Anesthesia in Normal and Anephric Patients

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deBROS FM, LAI A, SCOTT R, deBROS J, BATSON AG, GOUDSOUZIAN N, ALI HH, COSIMI AB, SAVARESE JJ. Pharmacokinetics and pharmacodynamics of atracurium during isoflurane anesthesia in normal and anephric patients. Anesth Analg 1986;65:743–6.

We compared the pharmacokinetics and pharmacodynamics of atracurium in eight normal and eight anephric patients during isoflurane anesthesia. Plasma concentrations were measured by high performance liquid chromatography after a single injection of 0.5 mg/kg, and neuromuscular effects were evaluated by the single twitch method. With regard to pharmacokinetic or pharmacodynamic parameters, we found no statistically significant differences between normal and anephric patients. We conclude that during isoflurane anesthesia, anephric patients distribute and eliminate atracurium much as normal patients do.

Key Words: NEUROMUSCULAR RELAXANTS—atracurium. PHARMACOKINETICS—atracurium. ANESTHETICS, VOLATILE—isoflurane. KIDNEY—failure.

Atracurium besylate (Tracrium) is a nondepolarizing muscle relaxant with an intermediate duration of action and a metabolic pathway unique to muscle relaxants. Clinically, Hofmann elimination seems to be the main breakdown process for this drug (1,2). However, more recent work has suggested that enzymatic hydrolysis by nonspecific plasma esterases is also involved and may be of greater importance (3,4). Studies in animals (5,6) and humans (7,8,9) have confirmed that both pathways are responsible for deactivating pharmacologically active atracurium in the systemic circulation. Consequently, normal kidney function does not seem essential for elimination of atracurium.

This paper presents the results of a study which supports the latter evidence. We evaluated the pharmacokinetics and pharmacodynamics of atracurium in normal and anephric patients under isoflurane anesthesia.

Method

Sixteen patients gave informed consent to the study, which received prior approval from the Institutional Review Board at Massachusetts General Hospital. Eight patients (ASA I or II) with normal renal function served as the control group. Eight patients (ASA II or III) without renal function served as the anephric group. All patients in the anephric group were scheduled for elective kidney transplant and were hemodialyzed within 24 hr prior to surgery. Premedication consisted of 5–10 mg diazepam orally, 1 hr prior to surgery. Anesthesia was induced with 4 mg/kg thiopental, and tracheal intubation was performed under 0.75–2.0% isoflurane and $N_2O–O_2$ anesthesia without the use of muscle relaxants. Ventilation was controlled and anesthesia maintained with 0.8% isoflurane in 60% N_2O and 40% O_2. The P_{CO_2} was maintained between 35 and 45 mm Hg as measured by end-tidal capnometry and the arterial pH and esophageal temperature was maintained within 34–37°C. Neuromuscular function was measured by recording the force of contraction of the adductor of the thumb with a Grass FT10 force displacement transducer. Supramaximal single twitch stimuli of 0.15 Hz were used to indirectly stimulate the ulnar nerve at the wrist using subcutaneous electrodes.
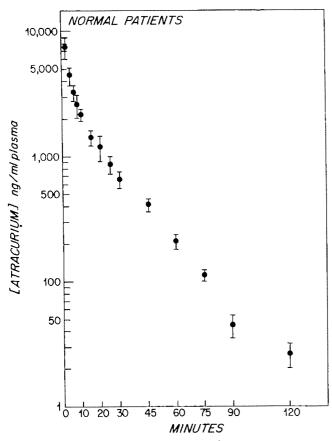
After stabilization of vital signs and the twitch response, atracurium besylate, 0.5 mg/kg, was injected over 20 sec. Blood samples for determination of plasma levels of atracurium were drawn 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 75, 90, and 120 min later. Samples were handled and analyzed according to a modification (10) of the method of Neill and Jones (11). Measurement
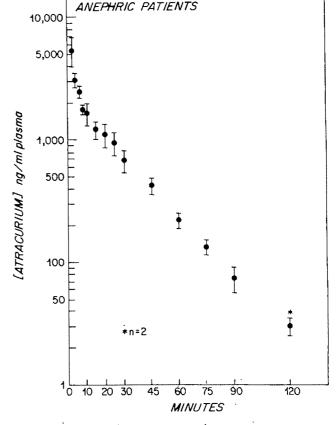
Figure 1. Plasma concentrations of atracurium measured 2–120 min after injection of 0.5 mg/kg at time zero N in eight normal patients.

Figure 2. Plasma concentrations of atracurium measured in anephric patients (n = 8) 2–120 min after injection of 0.5 mg at time zero. The exponential decay of the concentrations show that atracurium is virtually eliminated from plasma after 60 min.

of atracurium concentration in the systemic circulation has been fraught with difficulties, of which one is the continuous decay of atracurium in plasma outside the body if preventive steps such as acidification and freezing to −20°C are not performed rapidly. The plasma of each blood sample was immediately separated from the red cells by centrifugation in an Eppendorf 5414 bench model and transferred into glass vials prerinsed with 0.1N HCl. The plasma samples were then embedded in dry ice to facilitate quick freezing. The sensitivity of the assay was 10 ng/ml. Each set of plasma atracurium concentration vs time data was fitted to a biexponential equation that describes a two-compartment pharmacokinetic model with input into the central compartment and elimination from both compartments. The computer program NONLIN was used in the curve-fitting procedure, yielding values for four pharmacokinetic parameters (A, α, B, and β). The α and β half-lives were calculated by the relationship of ln 2 divided by the macroscopic rate constants (α and β), respectively. The clearance

(Cl) was calculated from the dose–area relationship and the volume of distribution (VDβ) was calculated by taking the ratio between Cl and β. Onset, duration, and recovery times were measured from the twitch recordings. In the statistical analysis, Student's t-test was used and $P \leq 0.05$ was considered statistically significant.

Results

The mean plasma decay curves for atracurium in normal and anephric patients are shown in Figures 1 and 2, respectively. There were no significant differences between the two groups in the major pharmacokinetic parameters, as can be seen in Table 1. Similar results were obtained in the comparison of pharmacodynamic data in the two groups (Table 2). Onset, duration of action, and recovery time were almost identical in the two groups and parallel to the behavior of the pharmacokinetic parameters. This observation is further supported by plotting the plasma levels of

Table 1. Pharmacokinetic Parameters Derived from a
Two-Compartment Model

Parameter	Normal (mean ± SEM)	Anephric (mean ± SEM)
A (ng/ml)	8770 ± 1620	7960 ± 2190
α (min^{-1})	0.30 ± 0.03	0.30 ± 0.07
B (ng/ml)	2500 ± 210	2100 ± 410
β (min^{-1})	0.04 ± 0.002	0.04 ± 0.004
$t_{1/2}\beta$ (min)	16.9 ± 0.8	21.1 ± 2.5
V_1 (L/kg)	0.05 ± 0.007	0.10 ± 0.028
Cl (ml/min/kg)	5.93 ± 0.64	6.89 ± 0.71
VDβ (L/kg)	141.9 ± 12.3	211.8 ± 31.0
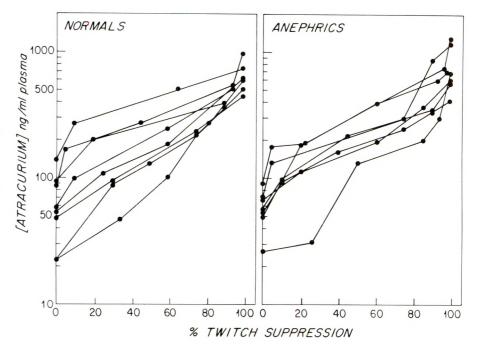
Abbreviations: A, zero time intercept; α, rate constant (distribution phase);
B, zero time intercept; β, rate constant (elimination phase); $t_{1/2}\beta$, half life; Cl,
clearance; V_1, volume of distribution (central); VDβ, volume of distribution
(steady state).

Table 2. Onset and Duration of Recovery After Injection
of 0.5 mg/kg Atracurium Intravenously in Normal and in
Anephric Patients

	Normal[a]	Anephric[a]
Onset (inj → max block)	2.3 ± 0.9	2.7 ± 0.9
Duration (inj → start recovery)	38 ± 8	37 ± 9
Duration (inj → 25% twitch recovery)	52 ± 10	52 ± 9
Duration (inj → 75% twitch recovery)	72 ± 17	73 ± 14
Duration (inj → 95% twitch recovery)	80 ± 18	80 ± 10
Duration (25% → 75% twitch recovery)	21 ± 8	21 ± 10

There are no statistically significant differences between the two groups.
[a]Min ± SD.

Figure 3. Recovery of twitch suppression
during the elimination phase of atracu-
rium from plasma in normal and anephric
patients. Each curve represents the data
points collected from each individual pa-
tient. The similarity of the two families of
curves show that the potency of atracu-
rium is no different in normal and ane-
phric patients.

atracurium vs twitch suppression during the elimi-
nation phase of the injection. The similarity of the
two families of curves in both normal and anephric
patients (Fig. 3) shows that the potency of atracurium
is no different either in normal or in anephric patients.

Discussion

This study demonstrates that during isoflurane anes-
thesia renal function has no specific effect on uptake,
distribution, and elimination of atracurium. The kid-
ney plays no significant role in the rate of decline of
plasma concentrations of atracurium following a sin-
gle injection. A two-compartment pharmacokinetic
model, with elimination from both compartments, was
used to describe the pharmacokinetic behavior of atra-
curium, because the drug is eliminated by two pro-
cesses (ester hydrolysis catalyzed by nonspecific es-
terases and degradation via Hofmann elimination) that
take place in the systemic circulation and the tissues
simultaneously. Although it was feasible to determine
the macroscopic rate constants (α and β), the micro-
scopic rate constants (k_{12}, k_{21}, k_{10}, and k_{20}) and the
volume of distribution at steady state (VD_{ss}) could not
be determined, because these latter parameters were
interdependent on each other mathematically. The
remaining pharmacokinetic parameters (e.g., clear-
ance, half-life, and volume of central compartment)

so obtained are useful to clinicians for estimation of dosage scheduling and for the determination of infusion rates for use in surgical procedures. Attempts to fit simultaneously the twitch and plasma atracurium data to the Hill equation were unsuccessful, because the best approach to such an analysis would require a constant rate infusion of the drug for 10–20 min, with frequent collection of blood samples and twitch data during this period.

The pharmacokinetics of atracurium were described first by Ward et al. in healthy anesthetized patients (7), and subsequently in unanesthetized patients (8) with severe hepatic and renal disease. The results of our study in anesthetized patients are similar to theirs. Our data obtained during isoflurane anesthesia also confirm the observation of Fahey et al. (9) that during halothane anesthesia the pharmacokinetics and pharmacodynamics of atracurium in anephric patients are no different than they are in normal patients.

It is recognized that the pharmacodynamics of neuromuscular relaxants may be affected by volatile anesthetic agents. Thus before the injection of atracurium we adjusted the concentration of isoflurane to each individual patient so that there was no somatic response to the incision. Thereafter, during maintenance of anesthesia the isoflurane concentration was kept constant at about MAC. This allowed us to satisfy the clinical needs of the patients and the constraints of the study. Not surprisingly, patients given slightly higher concentrations of isoflurane showed somewhat slower recovery of twitch suppression, but the mean values for both groups were not significantly different.

We conclude from this study that anephric patients distribute and eliminate atracurium much as normal patients do. Pharmacodynamic measurements show almost identical times for duration of and recovery from neuromuscular blockade in normal and anephric patients under isoflurane anesthesia. This study confirms previous observations indicating that atracurium appears to be a neuromuscular blocking agent well-suited for administration to patients in renal failure.

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The Dorsomedian Connective Tissue Band in the Lumbar Epidural Space of Humans:

An Anatomical Study Using Epiduroscopy in Autopsy Cases

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BLOMBERG R. The dorsomedian connective tissue band in the lumbar epidural space of humans. Anesth Analg 1986;65:747-52.

An anatomical study of the lumbar epidural space in 48 autopsy subjects was made using a method of endoscopy developed by the author called epiduroscopy. In every case there was a dorsal connective tissue band in the midline of the epidural space between the dura mater and the flaval ligaments. The appearance of the band varied from strands of connective tissue to a complete membrane. This connection fixed the dura mater to the flaval ligaments and also narrowed the epidural space in the midline.

Key Words: ANESTHESIA—epidural. ANATOMY, SPINAL CANAL—epidural space.

Although epidural anesthesia is a well-established anesthetic method, the anatomy of the epidural space and related structures is still a focus of research (1–3). Of particular interest is whether or not a dorsomedian fold of the dura mater exists (4–6). The lack of consensus on this point suggests that the methods presently available for anatomical studies are inadequate for a definitive exploration and visualization of the contents of the epidural space. As an alternative to other methods of investigation, the technique of epiduroscopy was developed for direct observation and photography of the lumbar epidural space.

Methods

During a period of 15 months, epiduroscopy was performed on 48 autopsy subjects aged 20–88 yr. The age and sex of the subjects are presented in Table 1. All findings were documented by photography.

Epiduroscopy was performed in a manner as similar as possible to that used for clinical epidural anesthesia. A few modifications of the method have been made since the technique was first described in a preliminary report (7). The endoscope used was a rigid, thin needle arthroscope, the Olympus Selfoscope. In the first seven cases model SES 1711 S was used with a diameter of 1.7 mm. In the remainder, model SES 2211 S was used, and its 2.2-mm diameter provided a greatly improved field of vision (Fig. 1). Each endoscope was equipped with a wide-angle Selfoc lens located at the tip and directed 90° to the longitudinal axis, with a window for emission of light transmitted from a light source by an optic cable. The depth of field was from 1 mm to infinity. A light source with a lamp of at least 250 watts was required. For photography the endoscope was attached to an Olympus 35 mm OM-2 camera; an adapter on the camera gave a magnification equivalent to that of a 105-mm lens.

Using an 18-gauge Tuohy needle (external diameter 1.2 mm), preferably in the L3–4 interspace, the lumbar epidural space was identified by loss of resistance to air. The distance to the epidural space was noted, and the Selfoscope was introduced with the aid of a trocar and a sheath in the adjacent cephalad lumbar interspace. Visual identification of the epidural space was made. By rotating the endoscope the epidural space could be observed in both a caudal and cranial direction. Small amounts of air, 2–3 ml at a time, were injected as necessary to open up the space. An epidural catheter (Vygon, diameter 1.0 mm) was introduced through the Tuohy needle during the epiduroscopy procedure. The epidural space was ob-

Table 1. Age and Sex Distribution of 48 Autopsy Subjects Submitted to Epiduroscopy

Age group (yr)	Men	Women	Total
20–29	1	—	1
30–39	1	—	1
40–49	2	3	5
50–59	6	3	9
60–69	5	6	11
70–79	6	6	12
80–89	5	4	9
Total	26	22	48

served with special attention to the amount and distribution of fat, blood vessels, and connective tissue.

Hospital records of all subjects were examined for information about previous epidural or subarachnoid anesthesia, diagnostic lumbar dural tap, or a history of spinal pathology of any type.

Results

At best, the epidural space could be visualized up to and including the next intervertebral space in both a cranial and caudal direction. Fat was seen in varying amounts in the epidural space, often occurring as isolated fat deposits in the connective tissue. Though difficulties were encountered in some cases, in 23 subjects it was possible to attempt to correlate the amount of epidural fat observed to the thickness of the subcutaneous fat layer measured directly through incisions at three locations: over the middle of the triceps muscle of the right arm; at the middle of the external part of the right thigh; and in the abdominal midline 4 cm distal to the umbilicus. No correlation was evident. Large amounts of fat did occur in very thin subjects, and small amounts occurred in obese subjects.

Despite the absence of circulation, blood vessels (filled veins) were often seen on the flaval ligaments, but no attempt was made to quantify the distribution of vessels. In a few cases blood vessels were also seen to cross the epidural space in the connective tissue.

Large amounts·of connective tissue were present in the epidural space in all cases, though with some variation. The connective tissue was distributed both dorsally and laterally. In *all* 48 cases there was a distinct dorsal connection in the midline between the dura mater and the flaval ligaments in the form of strands of connective tissue. This connection gave rise to a fixation of the dura mater to the flaval ligaments and also narrowed the epidural space in the midline (Figs. 2, 3, and 4). In some cases the connection was
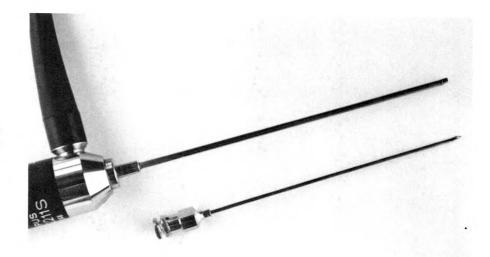
so tight that the dura mater was held very close to the flaval ligaments. The connection tended to be particularly well-developed in the region of the vertebral arches. In two cases, instead of strands there was a complete membrane in the dorsomedian sagittal plane that divided the epidural space and prevented the catheter from crossing over from one side to the other. These membranes could be followed over a distance of almost two lumbar segments. The dorsomedian connective tissue band caused a dorsomedian fold of the dura mater that was very distinct in 46 cases. In two cases such a fold could not be identified with certainty despite the clear presence of a connective tissue band.

The epidural catheter that was introduced in all 48 cases during epiduroscopy could be seen in 45 cases. In the other three cases movements of the connective tissue indicated the presence of the catheter, but the catheter itself was not visualized. In some instances the introduction of the epidural catheter was impaired by the dorsomedian fixation of the dura mater. In such instances, as the catheter passed out of the bevel of the Tuohy needle, it was seen to push against the dura mater, causing tenting of the dura mater until, after continued attempts to pass the catheter, it finally bent and then continued to pass into the epidural space. Sometimes the catheter could be seen to catch on strands of connective tissue causing changes in its direction, including a complete 180° turn. On three occasions where an excessive length of catheter (10–15 cm) was passed, the catheter could be seen to form several loops in the epidural space. In one instance the tip of the catheter dissected into the outer layer of the dura mater. In no instance did the catheter completely perforate the dura mater.
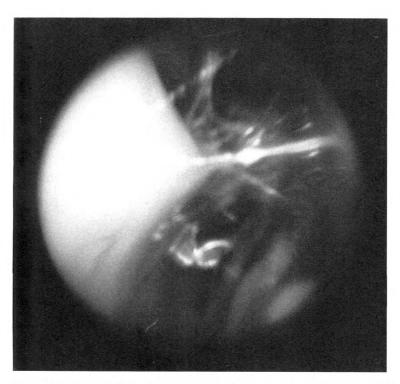
The pressure of the cerebrospinal fluid was measured in 17 subjects. It was zero in 13 cases and ranged from 4-9 cm H_2O in the other four subjects.
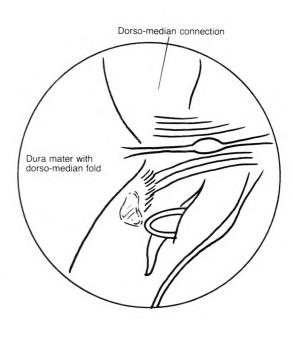
Complications of epiduroscopy included one accidental dural puncture with the Tuohy needle and three accidental dural taps with the endoscope or its trocar. In these four subjects the dorsomedian connection was found to be exceptionally heavy and the dura mater closely attached to the flaval ligaments. The endoscope caused a hemorrhage in one subject by traumatizing a vein. In three subjects small hemorrhages were caused by intensive manipulation with the catheter.

In order to make a rough estimation of the strength of the dorsomedian connective tissue band, it was subjected to mild trauma of the type that can be exerted during clinical epidural anesthesia by pushing or "stabbing" the catheter against the strands of connective tissue. All connections resisted at least three

Figure 1. Selfoscope SES 2211 S (above) together with 18-gauge Tuohy needle (below).

Figure 2. Subject 34. Left: Photograph of epidural space (caudad view) with bevel of Tuohy needle, dorsomedian connective tissue band, and dura mater with prominent dorsomedian fold. Photographic focus is imperfect because of technical difficulties in photographing the epidural space and limited depth of focus in the optic combination used. Right: Schematic drawing.

such "stabs". In some cases the connection was so strong that a forceful push with the endoscope against the dura mater was necessary to break the connection.
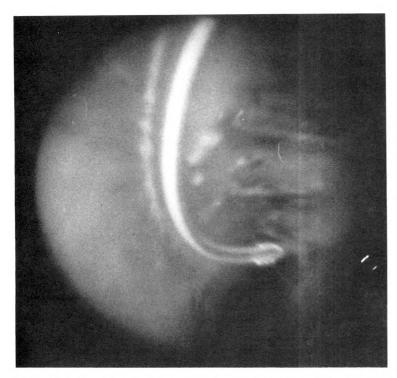
In three cases the epidural space was carefully dissected after epiduroscopy. The findings of fat and connective tissue mainly in the dorsomedian part of the epidural space were confirmed.
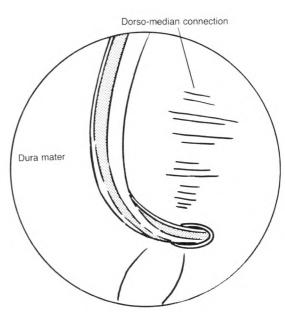
In 30 of the 48 cases there was a history of epidural or subarachnoid anesthesia, diagnostic lumbar dural tap, and/or a spinal pathology at one time or other. All events were included, even those occurring many years ago.

Discussion

An analysis of material based on autopsy specimens must always take into consideration possible artifacts that may limit the conclusions that can be drawn. In

Figure 3. Subject 36. Left: Photograph of epidural space (caudad view) with bevel of Tuohy needle, epidural catheter, and dorsomedian connective tissue band. See Figure 2 for note on photographic quality. Right: Schematic drawing.

the present study such factors include absence of circulation, low pressure of cerebrospinal fluid, postmortem autolysis, and trauma caused by manipulation of the epiduroscope. In this study the absence of circulation certainly influenced the appearance of vessels and a complete picture of their distribution could not be obtained. However large vessels were seen on the flaval ligaments with diameters that could easily accept an epidural catheter. The vessels that were seen to cross the epidural space in the connective tissue were estimated to have diameters of less than 1 mm. Traumatization of such vessels by the passage of the epidural catheter appeared possible.

The pressure of the cerebrospinal fluid in this study was low or nil, which is in general accordance with the study of Barison (8). The low pressure would tend to cause the dura mater to collapse, thereby accentuating the appearance of the dorsomedian connection and the observed dorsomedian fold of the dura mater.

A certain amount of postmortem autolysis is unavoidable. This will decrease the strength of the tissues encountered. Nevertheless, resistance to mild trauma of the type that can be expected in clinical epidural anesthesia was demonstrated in every case.

The introduction and manipulation of the epiduroscope may cause distortion of the epidural space. However, by taking care to avoid trauma when inserting and manipulating the epiduroscope, as well as in connection with injecting air into the epidural space, the distortion was initially minimal and the dorsomedian connective tissue band demonstrated in every case.
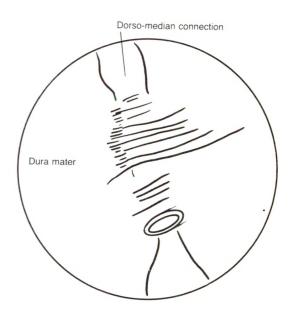
The principal contents of the epidural space have been known for many years (9, 10). However, studies of individual variations in various tissues within the epidural space do not seem to have been performed before. The variation in quantity of epidural fat could not be related in the present study to the amount of subcutaneous fat in the cases in which such measurements were made. In the literature, hormonal influences have been said to affect the fat content of the epidural space, and these influences may be more important than the general fat content of the body (11).

The dorsomedian connective tissue band that was demonstrated in every subject in this study fixed the dura mater to the flaval ligaments and narrowed the epidural space in the midline. This appearance contradicts the opinion that the epidural space is widest in the dorsal midline (12).

In the present study an interesting observation was that although the Tuohy needle was introduced in the midline, it often appeared slightly to one side in the epidural space adjacent to the dorsomedian connection.

The dorsomedian connective tissue structure ob-

Figure 4. Subject 48. Left: Photograph of epidural space (caudad view) with bevel of Tuohy needle and heavy dorsomedian connective tissue band. See Figure 2 for note on photographic quality. Right: Schematic drawing.

served in this study with epiduroscopy was also hypothesized in 1963 by Luyendijk (4), who, in presenting the results of peridurography, described a central defect of the contrast medium. He ascribed the defect to a dorsomedian fold of the dura mater and assumed that the fold was caused by median attachments of the dural sac to the vertebral laminae. The fold was subsequently discussed further by Lewit and Sereghy (5) and again by Luyendijk (6). Husemeyer and White (1) successfully made polyester resin casts of the epidural space in eight autopsy subjects and demonstrated in five of them a distinctly triangular shape of the lumbar dural sac with the apex dorsomedial. In some of these preparations the angle of the apex was so acute that it justified description as a dorsomedian fold of the dura mater. On the other hand, Harrison et al. (3) also made casts of the epidural space in one group of ten autopsy specimens and of both the subarachnoid and epidural spaces in another group of ten subjects, but could demonstrate a dorsomedian fold of the dura mater in only one subject and that in the latter group. In the present study the dorsomedian fold was distinctly seen in all but two cases, and the dorsomedian connective tissue band was clearly present even in these two cases. The fold was plainly caused by a dorsomedian connective tissue band attaching the dura to the flaval ligaments, and it was accentuated by the low pressure of the

cerebrospinal fluid. In my first 30 epiduroscopies (7), where saline instead of air was injected into the epidural space, the dorsomedian fold could not be demonstrated with certainty. The change of technique in the material presented here—using air for injection and using an endoscope with a larger diameter—facilitated conditions for observation and this structure could be visualized.

The origin of the dorsomedian connective tissue band remains to be established. Anatomical textbooks report the presence of ventral connections between the dura mater and the posterior longitudinal ligament but usually do not mention the existence of dorsal attachments (13, 14). Posterior fibrous connections have been mentioned by Anson and McVay (15). The dorsomedian connective tissue band demonstrated in this material may be of the same origin as the ventral connection, and may be congenital. In this regard it is necessary to consider factors that might influence the amount of connective tissue and its appearance. Thus the hospital records of the subjects were examined for a history at any time of epidural or subarachnoid anesthesia, diagnostic lumbar dural tap, or spinal pathology of any type. There was no history of any of these factors in 18 cases, more than one third of the total material. This finding favors the concept that the dorsomedian connection is not an acquired anatomical structure.

The existence of the dorsomedian connection might help to explain some of the unexpected events that may occur during clinical epidural anesthesia, e.g., accidental dural puncture and an uneven onset and spread of anesthesia. In the future the method of epiduroscopy may be of help in developing epidural anesthetic techniques. Epiduroscopy may also prove useful in the extraction of an accidentally severed epidural catheter.

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Venous Blood Concentrations after Subarachnoid Administration of Bupivacaine

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AXELSSON KH, SUNDBERG AEA, EDSTRÖM HH, WIDMAN GB, SJÖSTRAND UH. Venous blood concentrations after subarachnoid administration of bupivacaine. Anesth Analg 1986;65:753–9.

Peripheral venous blood concentrations of bupivacaine were measured in 51 patients given 0.5% (4 ml, 20 mg) or 0.75% (3 ml, 22.5 mg) bupivacaine, both solutions with or without glucose, for spinal anesthesia. The initial absorption of bupivacaine, as measured in peripheral venous blood, was rapid, although the blood concentrations were low. The mean peak concentration (C_{max}) did not differ when glucose was added to 0.5 or 0.75% bupivacaine. When glucose-free and glucose-containing bupivacaine groups were combined, 22.5 mg bupivacaine give a significantly higher venous blood

concentration than 20 mg of the solution. The mean time between subarachnoid injection and the time when C_{max} was reached (t_{peak}) was influenced by the density of bupivacaine, i.e., the t_{peak} of bupivacaine with glucose was significantly shorter than with glucose-free solution (35 min; $P < 0.05$). No correlation was found between C_{max} and the age, height, or weight of the patients, or between C_{max} and the maximum cephalad level of analgesia in the different groups. In addition, there was no correlation between t_{peak} and the age, height, or weight of the patients. The maximal cephalad level of analgesia did not influence t_{peak} in the different groups (the correlation coefficients < 0.3).

Key Words: ANESTHETIC TECHNIQUES—spinal. ANESTHETICS, LOCAL—bupivacaine.

The systemic effects of a local anesthetic are closely related to its concentration in the blood or plasma, which in turn is influenced by factors such as the site of injection, total dosage, addition of vasoconstrictor, and the intrinsic pharmacologic characteristics of the local anesthetic (1–4). There are numerous reports of blood levels of lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine after intravenous and epidural administration (1–3,5–7), but only limited information is available concerning the absorption of local anesthetics after subarachnoid administration (8–10).

The introduction of bupivacaine as a spinal anesthetic agent has been associated with increased interest in spinal anesthesia. Recent studies have shown that glucose-free bupivacaine produces a significantly longer duration of motor block than a glucose-containing solution, regardless of whether the spinal injection is performed with the patient in sitting position (11–14) or in horizontal lateral position (15). With

the patient in sitting position during subarachnoid injection, the duration of analgesia is increased when glucose-free bupivacaine is given (12,13,14). When using hyperbaric solution it has been reported that 0.75% bupivacaine (22.5 mg) produces a more marked effect on the blood pressure than hyperbaric 0.5% bupivacaine (20 mg) or isobaric 0.75% bupivacaine (22.5 mg) (12). Similarly, the question arises as to whether the absorption of bupivacaine from the subarachnoid space is dependent on the concentration/dosage and the density of the solution. The main purpose of the present investigation was to measure and compare the absorption of bupivacaine after spinal administration of hyperbaric and glucose-free solutions as expressed by the length of time from the subarachnoid injection until the peak concentration in the blood (C_{max}) was reached (t_{peak}). An additional aim was to compare 0.75% and 0.5% of bupivacaine with respect to C_{max}.

Patients and Methods

The study comprised 51 patients, ASA I and II, randomly allocated to five groups (Table 1) and in most cases scheduled for urological surgery under spinal anesthesia. Patients with spinal deformities, mental disturbances, or neurological diseases were excluded.

Table 1. Bupivacaine Solutions and Doses Used in the Different Groups

| Group | Anesthetic concentration | Anesthetic amount | | Glucose | Position |
		ml	mg		
B-0.5 + Gl	Bupivacaine 0.5%	4	20	8%	Sitting
B-0.5	Bupivacaine 0.5%	4	20	0%	Sitting
B-0.75 + Gl	Bupivacaine 0.75%	3	22.5	8%	Sitting
B-0.75	Bupivacaine 0.75%	3	22.5	0%	Sitting
B-0.75ᵃ	Bupivacaine 0.75%	3	22.5	0%	Horizontal lateral

ᵃHorizontal lateral position.

Table 2. Patient Characteristics

Group	n	Ageᵃ (yr)	Age range (yr)	Heightᵃ (cm)	Height range (cm)	Weightᵃ (kg)
B-0.5 + Gl	11	69 ± 6.0	58–79	172 ± 4.6	167–180	72 ± 7.3
B-0.5	10	71 ± 7.9	57–78	175 ± 8.2	165–191	75 ± 7.6
B-0.75 + Gl	10	70 ± 10.4	58–89	173 ± 7.9	155–183	73 ± 10.8
B-0.75	10	69 ± 6.6	60–80	175 ± 6.0	165–181	76 ± 5.7
B-0.75ᵇ	10	68 ± 7.3	56–83	173 ± 9.8	156–185	77 ± 10.1

ᵃValues are mean ± SD.
ᵇHorizontal lateral position.
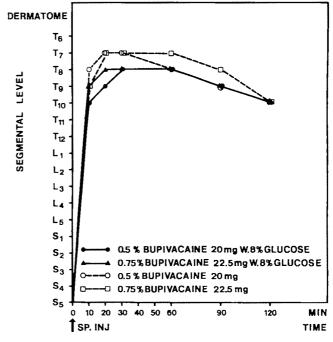
The age, weight, and height of the patients were comparable in the different groups (Table 2). The patients gave their written informed consent to the study, which was approved by the Ethics Committee of the Örebro Medical Center Hospital.

Patients were premedicated with opiates combined with scopolamine or promethazine. Immediately before the spinal injection, 0.5 mg atropine was given intravenously. Premedication was performed in a standardized manner based on the patients' weight. There were no significant differences among the groups.

The dural puncture was performed at the L2-3 or L3-4 interspace using a 22-gauge spinal needle with the patient in the sitting or horizontal lateral position (Table 1). The bevel of the needle was directed laterally during the puncture, which was performed in the midline. Bupivacaine, either in a glucose-free or hyperbaric (8% glucose) solution, was used, and 4 ml of 0.5% (20 mg) or 3 ml of 0.75% bupivacaine (22.5) was given. The density of the glucose-free solutions was 1.000 at 37°C, with a pH of 5.0–6.0. When 8% (80 mg/ml) glucose was added to the bupivacaine solution the density was 1.026 at 37°C with a pH of 4.0–6.0.

The speed of the injection was 0.5 ml/sec. The patients who were sitting during the injection remained sitting for 2 min and were then placed in the lithotomy position. Those patients who were in the horizontal lateral posture during injection were placed in the lithotomy position immediately after the injection.

All patients were given 500 ml of lactated Ringer's

Figure 1. Segmental spread of analgesia during the first 2 hr. There were no significant differences between the bupivacaine groups. The spread of analgesia was the same whether 0.75% bupivacaine (22.5 mg) was given in the horizontal lateral position or in the sitting position. The curve of analgesia representing 0.75% bupivacaine given in the horizontal lateral position is excluded.

solution immediately before the dural puncture. Any decrease in systolic blood pressure of more than 30% was treated by intravenous administration of vasopressor (Etilephrinum, INN, Boehringer-Ingelheim).

Venous blood samples were collected from a pe-

Figure 2. Mean (± SEM) blood concentrations of bupivacaine after subarachnoid administration of 20 mg (4 ml) of glucose-free and hyperbaric 0.5 mg bupivacaine. There is no significant difference between the groups.
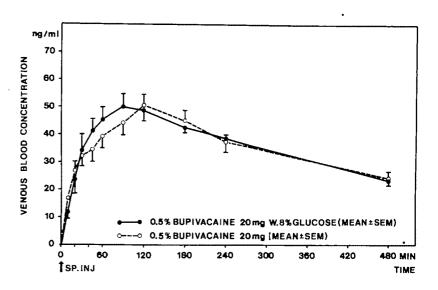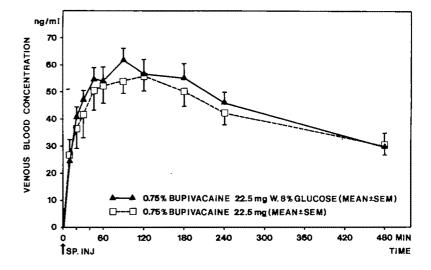
Figure 3. Mean (± SEM) blood concentrations of bupivacaine after subarachnoid administration of 22.5 mg (3 ml) of glucose-free and hyperbaric 0.75% bupivacaine. There is no significant difference between the groups.

ripheral vein before and 10, 20, 30, 45, 60, 90, 120, 180, 240 and 480 min after subarachnoid administration of the local anesthetic. The samples were kept deep-frozen at −20°C until analyzed.

Drug concentrations in whole blood were determined at Astra Läkemedel AB, Södertälje, according to the method described by Caldwell et al. (16), but with the following modifications: mass fragmentography was carried out using an LKB 2091 GC/MS equipped with an LKB 2091-710 Multiple Ion Detector; the column was a 1.5 m glass column packed with 3% JXR on Gas Chrom Q (100–120 mesh); the column temperature was 250°C, and the retention times for bupivacaine and the internal standard were 2.0 and 2.3 min, respectively. The C_{max} and t_{peak} were determined for each patient. At the same time as the blood samples were collected, the cephalad and caudal levels of analgesia were determined by the pin-prick method on the trunk 10–15 cm on either side of the

midline, and also on the perineum and the lower extremities.

Statistics

Analysis of variance was used in judging the statistical significance of differences between treatment groups. Regression analysis was used for measuring the relation between variables. The P values reported refer to two-tailed tests, and $P < 0.05$ was considered statistically significant.

Results

Spinal anesthesia was satisfactory for surgery in all patients. The cephalad and caudal levels of analgesia were similar in all groups: 14–16 segments were involved, corresponding to dermatomes T6–T8 to S5 (see Fig. 1). There was no correlation between max-
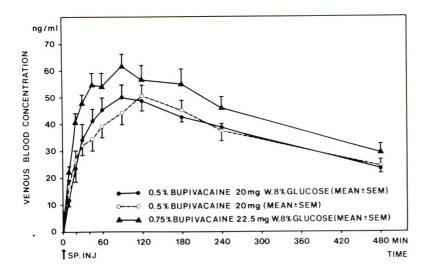
Figure 4. Mean ($\pm$ SEM) blood concentrations of bupivacaine after subarachnoid administration of 20 mg of glucose-free (0.5%) and 20–22.5 mg of hyperbaric (0.5%–0.75%) bupivacaine.

Table 3. Peak Concentrations of Bupivacaine in the Blood (C_{max}) and Lengths of Time from the Subarachnoid Injection to C_{max} (t_{peak})

	C_{max} (ng/ml)			t_{peak} (min)		
Group	Mean $\pm$ SD	Median	Range	Mean $\pm$ SD	Median	Range
B-0.5	52 $\pm$ 11.4	54	36–73	135 $\pm$ 30.7	120	90–180
B-0.5 + Gl	56 $\pm$ 15.4	53	37–83	98 $\pm$ 53.8	90	30–240
B-0.75 + Gl	68 $\pm$ 14.5	68	38–89	87 $\pm$ 41.0	90	45–180
B-0.75	69 $\pm$ 27.9	66	49–129	119 $\pm$ 72.4	90	30–240
B-0.75[a]	95 $\pm$ 58.4	79	31–221	126 $\pm$ 69.0	120	30–240

[a]Horizontal lateral position.

imum cephalad spread of analgesia and C_{max}/t_{peak} in the different groups.

The blood concentration curves of bupivacaine were similar in all groups regardless of the density of the solution or of the concentration/dosage (Figs. 2–5). The onset of systemic absorption, as measured in peripheral venous blood, was rapid. Thus 10 min after subarachnoid adminstration bupivacaine was detected in the venous blood in 46 of 51 patients; 20 min later the mean concentrations varied from 65 to 85% of C_{max} in the different groups. The peak values were reached approximately 90 min after spinal injection of the hyperbaric solutions and after 120 min in those given glucose-free solutions (Figs. 2–4). There were large interindividual variations in the venous blood concentrations, especially after administration of 22.5 mg of glucose-free bupivacaine with the patients in the horizontal lateral position (Table 3, Fig. 5). The maximal venous blood concentration seen in any patient was 221 mg/ml (0.22 μg/ml).

With the patients in the sitting position during the spinal injection, t_{peak} varied from 87 to 135 min (Table 3). The difference in mean t_{peak} values between the glucose-free and glucose-containing solutions was 37 min with 0.5% bupivacaine and 32 min with a 0.75%

solution. When the results obtained with the 0.5% and the 0.75% solutions were combined, the average difference in t_{peak} was 34.5 min. This average difference (34.5 min) differs significantly from zero.

In addition, there was a significant difference between the 0.75% and the 0.5% bupivacaine solutions with respect to C_{max}. When trials in which glucose was used were considered separately, the difference in C_{max} between 0.75% and 0.5% bupivacaine was 12 ng/ml. The corresponding difference for the glucose-free solutions was 17 ng/ml. When, on the other hand, the results for both glucose-free and glucose-containing solutions were combined, the mean difference in C_{max} between 0.75% and 0.5% bupivacaine was 14.5 ng/ml. This mean difference is statistically significant.

No correlation was found between C_{max} and the age, height and weight of the patients. Neither was there any correlation between t_{peak} and age, height and weight of the patients (the correlation coefficient <0.3).

The mean decrease in systolic blood pressure was 10–20%. A decrease in blood pressure exceeding 20% was observed in three or four patients in each group (Table 4). Hyperbaric 0.75% bupivacaine did not produce a more marked effect on the blood pressure

Figure 5. Mean (± SEM) blood concentrations of bupivacaine after subarachnoid administration of 20 mg (4 ml) of glucose-free or hyperbaric 0.5% bupivacaine and 22.5 mg (3 ml) of glucose-free 0.75% bupivacaine injected with the patients in the sitting or in the horizontal lateral position.

Table 4. Frequency of Reductions in Systolic Blood Pressures

Decrease in systolic blood pressure (%)	Group				
	B-0.5 + Gl	B-0.5	B-0.75 + Gl	B-0.75	B-0.75[a]
<10	4	3	1	2	3
10–20	2	3	6	5	3
20–30	1	4	1	2	2
>30	3	—	2	1	2

[a]Horizontal lateral position.

than the other solutions tested. The patients given a vasopressor agent during the first hour were equally distributed among the groups (2–3 patients in each group). There was no correlation between the time of the maximum decrease in blood pressure and t_{peak}.

Discussion

Bupivacaine is a useful spinal anesthetic agent in dosages of 15–22.5 mg, both in a glucose-free and hyperbaric solution (12,13,18,19). It has been reported to be 4–5 times as toxic as mepivacaine and lidocaine and to be about equal in toxicity to tetracaine (20–22).

In this study, the bupivacaine concentration was determined in venous blood. It is reported that arterial blood concentrations of local anesthetics are significantly higher than the venous blood level during the initial 60 min following drug injection (23). However, the bupivacaine concentration in the whole blood does not reach its maximum until 90–120 min after the spinal injection, and the difference between arterial

and venous blood concentrations is minimal at that time. Therefore venous blood sampling was chosen. The bupivacaine concentration was determined in whole blood, not in plasma. Bupivacaine, which is highly protein bound, shows marked differences when plasma and whole blood concentration are compared. The relationship is as follows (23): (whole blood concentration) = 0.5/(plasma concentration). Toxic plasma concentrations of bupivacaine are reported to be 2–4 μg/ml (22,24) which correspond to whole blood concentrations of 1–2 μg/ml.

In a number of investigations it has been shown that the addition of glucose to bupivacaine solution to make it hyperbaric alters the local anesthetic profile of the drug when used for spinal anesthesia. The duration and frequency of complete motor blockade of the lower limbs decrease and the duration of analgesia is shortened (11–15). In order to study whether addition of glucose also affected the systemic absorption of bupivacaine, the venous blood concentrations were measured after subarachnoid administration of both 0.5% and 0.75% bupivacaine in glucose-free ("isobaric") and hyperbaric solution. The subarachnoid injections were performed in a standardized manner with the patients in the sitting position. In one group the spinal injection was performed with the patients in the horizontal lateral position to determine if the position of the patient had any influence on the systemic absorption of bupivacaine. All blockades resulted in sufficient surgical anesthesia.

The blood concentrations were very low regardless of the dosage/concentration and the density of the

local anesthetic solution. The blood levels of lidocaine have also been shown to be low after subarachnoid administration (8–10). It has been proposed that some physiological responses to epidural anesthesia are related to blood levels of the local anesthetic. The blood concentrations of bupivacaine after subarachnoid administration should be too low to exert such effects. The highest venous blood concentration of bupivacaine in the present study was 0.22 μg/ml, which is between one-tenth and one-fifth of that reported to be associated with toxic reactions in man (22,24).

No difference was found between C_{max} values after administration of glucose-free and hyperbaric solutions regardless of whether a dose of 20 or 22.5 mg of bupivacaine was used, and this result agrees with data from Burm et al. (10). Increasing dosage should result in higher blood concentrations. In fact when both hyperbaric and glucose-free solutions were considered, administration of 22.5 mg resulted in a significantly higher venous blood concentration than 20 mg (Table 3). Regardless of dosage the blood concentration was low, and in clinical practice the difference is of minor importance.

It was found that the blood concentrations of bupivacaine tended to be higher in patients who lay in the lateral position during administration of the local anesthetic than in those injected in the sitting position. However, the difference was not statistically significant, and there were rather more marked interindividual differences in the supine group than in the sitting group.

With hyperbaric solutions (including 20 and 22.5 mg), t_{peak} was significantly shorter than with glucose-free solutions. These results agree with those of Burm et al. (10), who found significantly shorter t_{peak} values after administration of hyperbaric than of glucose-free 0.5% bupivacaine (15 mg), which suggests more rapid systemic absorption after administration of a hyperbaric solution. On the other hand, it has been reported from animal studies that the rate of absorption from the cerebrospinal fluid increases with decreasing density of the local anesthetic solution (25). The present study indicates that the density of the solution affects the rate of absorption of bupivacaine in some way that might possibly explain some but not all of the differences in anesthetic effect between hyperbaric and glucose-free solutions after subarachnoid administration.

The absorption of lidocaine has been reported to be slower from the subarachnoid than from the epidural space (8). In the present study t_{peak} for bupivacaine was 1.5–2 hr, which is slower than the 20–30 min that has been observed after epidural administration (26,27).

In the present study no correlation was found between age and C_{max}, which contrasts with the result of an earlier study (9) showing a positive correlation between age and venous blood concentrations after subarachnoid administration of lidocaine (higher concentrations in older patients). Although this could be due to differences in the physicochemical properties of the local anesthetic agents, the present data do not support the general hypothesis that an increased duration of spinal anesthesia with age is due to a decrease in systemic absorption of the local anesthetic (28).

It could be expected that the more cephalad the level of sensory denervation, the greater the area of absorption in the subarachnoid space and, consequently, the higher C_{max}. No correlation was found between C_{max} and the maximum cephalad spread of the blockades as determined by pin-prick. Another interesting finding was the lack of correlation between height and venous blood concentration (C_{max}/t_{peak}), i.e., the absorption did not differ between tall and short patients.

In conclusion, after subarachnoid administration of bupivacaine the C_{max} values were low and t_{peak} relatively high. Hyperbaric bupivacaine solution (20 and 22.5 mg) was associated with statistically shorter t_{peak} than the glucose-free solution. A larger dosage (22.5 mg) resulted in a significantly higher C_{max} than a lower dosage (20 mg). When used for spinal anesthesia, bupivacaine seems to be a safe local anesthetic, as the C_{max} values were 5–10 times lower than those reported to result in systemic toxicity in man.

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Comparison of pH-Adjusted Lidocaine Solutions for Epidural Anesthesia

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Anesth Analg 1986;65:760-4.

One hundred forty-eight adult patients having epidural anesthesia for cesarean section, postpartum tubal ligation, lower extremity orthopedic procedures, or lithotriptic therapy were assigned to five groups. Group 1 patients were given a commercially prepared 1.5% lidocaine solution with 1:200,000 epinephrine plus 1 ml of normal saline per 10 ml of lidocaine; the solution pH was 4.6. Group 2 patients were given commercially prepared 1.5% lidocaine solution plus 1:200,000 epinephrine, with 1 mEq (1 ml) NaHCO₃ per 10 ml of lidocaine; the solution pH was 7.15. Group 3 patients received the commercial solution of 1.5% lidocaine with 1:200,000 epinephrine; the solution pH was 4.55. Group 4 patients were given a mixture of 18 ml of 2% lidocaine with 30 ml of 1.5% lidocaine, both commercially packaged with 1:200,000 epinephrine, plus 1 mEq (1 ml) of NaHCO₃ added per 10 ml of solution; the solution pH was 7.2. Group 5 patients received 1.5% plain lidocaine to

which epinephrine was added to a final concentration of 1:200,000; the solution pH was 6.35. Times of onset of analgesia (time between the completion of the anesthetic injection and loss of scratch sensation at the right hip (L-2 dermatome)) and of surgical anesthesia (time between completion of injection and loss of discomfort following tetanic stimulation produced by a nerve stimulator applied to skin on the right hip) were significantly more rapid in the groups that received the pH-adjusted solutions (groups 4 and 2). Group 4 had the fastest mean onset time, 1.92 ± 0.17 min, followed by group 2, 3.31 ± 0.23 min. Onset times were progressively longer in group 5 at 4.27 ± 0.51 min, group 3 at 4.73 ± 0.37 min, and group 1 at 7.11 ± 0.82 min. The spread of sensory blockade was also significantly more rapid in the pH-adjusted groups 5, 10, and 15 min after epidural injection. In patients having cesarean sections in groups 1 and 2, plasma lidocaine levels in the maternal peripheral venous and in umbilical cord blood and Apgar scores were similar in both groups.

Key Words: ANESTHETICS, LOCAL—lidocaine. ANESTHETIC TECHNIQUES—epidural.

Onset of local anesthesia of a nerve occurs when a drug such as lidocaine enters the nerve axoplasm and attaches itself within the sodium channel of the nerve (1,2). To reach this active site, the drug must traverse both the perineural sheath and nerve membrane, structures permeable to the drug only in its nonionized form.

To achieve drug solubility and stability, commercial preparations of local anesthetics are prepared as local anesthetic salts, all of which are consistently acidic, those with epinephrine being even more acidic (3). In solution, the fraction of lidocaine present in its nonionized form varies from less than 1% when the pH of lidocaine solution is below 6 to 11% at pH 7. Increasing the pH of the local anesthetic solution toward the physiologic range has been reported to improve the quality of neural blockade in vitro (4). In a preliminary clinical report, Galindo demonstrated rapid times of onset of neural blockade in patients receiving local anesthetics to which increments of sodium bicarbonate were added (5).

This study was undertaken to determine the effect of increasing the pH of the lidocaine solutions used for epidural administration on time of onset of local anesthesia and attainment of surgical anesthesia. The effect of pH on vascular absorption of lidocaine from the epidural space in patients undergoing cesarean sections was also evaluated.

Methods

This investigation was approved by our hospital's Human Investigation Committee and was carried out in 148 adult patients having an epidural anesthetic. These
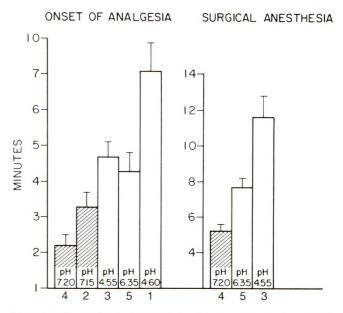
Table 1. Effect of pH and Concentration on Onset of Epidural Analgesia

Group	n	Anesthetic mixture	Lidocaine Concentration	pH	Analgesia onset (min)
1	36	Commercial 1.5% lidocaine with 1:200,000 epinephrine and 1 ml/10 ml added normal saline	1.37%	4.60	7.11 ± 0.82
2	35	Commercial 1.5% lidocaine with 1:200,000 epinephrine and 1 mEq/10 ml added NaHCO₃	1.37%	7.15	3.31 ± 0.23
3	29	Commercial 1.5% lidocaine with 1:200,000 epinephrine	1.5%	4.55	4.73 ± 0.37
4	28	18 ml of 2% lidocaine plus 30 ml of 1.5% commercial with 1:200,000 epinephrine with 1 mEq/10 ml added NaHCO₃	1.5%	7.20	1.92 ± 0.17
5	20	1.5% lidocaine with 1:200,000 epinephrine added at time of injection	1.5%	6.35	4.27 ± 0.51
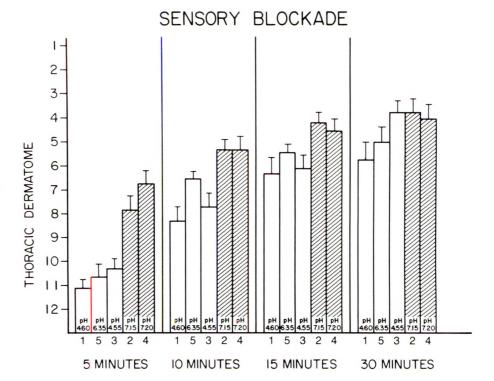
patients were divided into five groups (Table 1). Patients were randomly assigned to groups 1 and 2 based upon the last digit in their hospital identification number, and all of the remaining groups were sequentially done. In all cases the patients and the evaluator were blinded as to which anesthetic was used. Each group was composed of patients having cesarean sections, postpartum tubal ligation, lower extremity orthopedic procedure, or lithotripic treatment. Patients were placed in a right lateral decubitus position, and the epidural space was located using a loss of resistance method. Twenty milliliters of local anesthetic was injected in patients having cesarean sections or postpartum tubal ligations; 25 ml was injected in all others. Injection was done in 5 ml increments every 20–30 sec. An epidural catheter was then introduced and the patients were quickly turned to the supine position. The local anesthetic solutions were as follows; group 1 received a commercially prepared 1.5% lidocaine solution with 1:200,000 epinephrine plus 1 ml of normal saline per 10 ml of lidocaine; group 2 received a commercially prepared 1.5% lidocaine solution with 1:200,000 epinephrine plus 1 mEq (1 ml) NaHCO₃ per 10 ml of lidocaine; group 3 received the commercial solution of 1.5% lidocaine with 1:200,000 epinephrine; group 4 received a mixture of 18 ml of 2% lidocaine with 30 ml of 1.5% lidocaine, both commercially packaged with 1:200,000 epinephrine plus 1 mEq (1 ml) of NaHCO₃ added per 10 ml of solution; and group 5 received 1.5% plain lidocaine to which epinephrine was added to a final concentration of 1:200,000. All solutions were prepared just prior to use.

Time of onset of analgesia was defined as the time between the completion of the anesthetic injection and loss of scratch sensation at the right hip (L-2 dermatome). The level of analgesia (to scratch) was assessed in the midline 5, 10, 15, and 30 min after injection. Surgical anesthesia was defined as loss of discomfort after tetanic stimulation by a nerve stim-

Figure 1. Times for onset of analgesia to scratch and onset of surgical anesthesia as measured with a nerve stimulator in each group together with the pH of the lidocaine epidural solution used in each group.

ulator (Professional Instrument Company Model NS3A, tetanic output equal to 25 volts direct current across a 1000 ohm load at 50 Hz) applied to alcohol-prepared skin on the right hip. If the level of analgesia after 15 min was inadequate (less than T-6), increments of 5 ml of the original solution were injected via the epidural catheter. Patients receiving further injections of drug were not included in the 30-min evaluations. Gas chromatographic evaluation (6) of lidocaine plasma levels was determined prior to epidural injection and at 5, 10, 15 or 30 min in groups 1 and 2 patients having cesarean sections. Apgar scores (1 min and 5 min) and umbilical cord lidocaine levels were determined in infants delivered from the cesarean section patients. All data were subjected to analysis of variance and a $P \leq 0.05$ was considered statistically significant.

SENSORY BLOCKADE

Figure 2. The highest levels of sensory blockade in each group, along with the pH of the injected solution.

Results
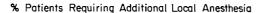
The time of onset of analgesia was inversely related to the pH of the epidural lidocaine solution injected (Fig. 1). The shortest mean onset times for sensory analgesia occurred in patients receiving a lidocaine solution in which the pH was adjusted to 7.15–7.20. The most rapid onset occurred in group 4 (1.5% lidocaine with 1:200,000 epinephrine at pH 7.2), which at 1.9 min was significantly faster than all other groups. The second fastest onset time of 3.3 min occurred in group 2 (1.37% lidocaine with 1:200,000 epinephrine at pH 7.15). Onset of analgesia was significantly delayed when the more acidic local anesthetic solutions were used (groups 1, 3, and 5). Group 5 (1.5% plain lidocaine to which epinephrine was added to 1:200,000 to give a solution with a pH of 6.35) had an onset time of 4.3 min. Group 3 (1.5% lidocaine commercially prepared with 1:200,000 epinephrine, giving a solution pH of 4.55) had an onset time of 4.7 min (no significant difference between groups 5 and 3). Group 1, the most dilute and acidic solution (pH 4.60), had a longer onset time for analgesia at 7.1 min than any of the other groups.
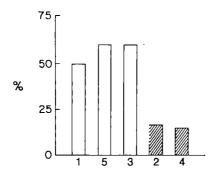
Onset of surgical anesthesia in patients who received 1.5% concentrations of lidocaine with epinephrine (groups 3, 4, and 5) was also inversely related to pH (Fig. 1) (groups 1 and 2 received lidocaine concentrations of 1.37%). The shortest time to loss of painful sensation with tetanic stimulation applied to the right hip was 5.2 min in group 4, followed by group 5 at 7.6 minutes ($P < 0.05$). Groups 4 and 5 achieved surgical anesthesia significantly more rapidly than group 3 (11.5 min) ($P < 0.05$).

Greater spread of sensory blockade also was apparent at 5, 10, and 15 min in the solutions that had been pH-adjusted with $NaHCO_3$ (groups 2 and 4). For instance, at 5 and 10 min, group 4 had a sensory level of T6.7 and T5.3, respectively; group 2 had a sensory level of T7.9 and T5.3. These values contrast with group 3, which had a sensory level of T10.5 and T8.2 ($P \leq 0.05$) (Fig. 2). However, at 30 min the sensory level was not significantly different among groups 2, 3, 4, and 5. Because pH-adjusted groups achieved higher sensory levels more rapidly, additional doses to achieve adequate analgesia were required with less frequency (Fig. 3). For instance, patients in groups 2 and 3 required additional injections of lidocaine in only 15–18% of cases while patients in groups 1, 3, and 5 required additional doses in 50–62% of the cases.

Plasma lidocaine levels measured in mothers having cesarean sections in groups 1 and 2 were not significantly different (Fig. 4). The 1- and 5-min Apgar scores in infants delivered to mothers in these two groups were likewise not significantly different. Mean time from epidural injection to delivery was similar for infants in group 1 (34.1 ± 7.5 min) and group 2 (36.5 ± 5.1 min).

% Patients Requiring Additional Local Anesthesia
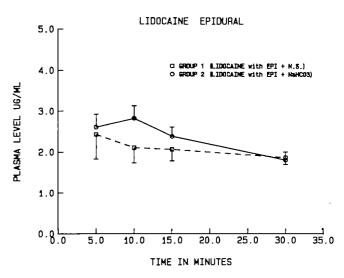
Figure 3. The percent of patients that required additional doses of local anesthetic in each group.

Figure 4. The plasma lidocaine concentrations after epidural administration in mothers at cesarean section are shown for groups 1 and 2.

Discussion

The present study demonstrates that the onset of epidural analgesia and the establishment of surgical anesthesia are inversely related to pH. These observations are not surprising. The classic studies in vitro by Ritchie et al. (7–9) provide the basis for adjusting the pH of local anesthetic injected as done in this study. Local anesthetic solution applied to a nerve membrane exits in two forms: the nonionized freebase and the charged ionized cation. The percentage of the nonionized form can be predictably increased by increasing the pH of the solution. Calculation of the levels of ionized and nonionized forms can be done simply by using the Henderson–Hasselbach equation. An increase in the nonionized fraction of the local anesthetic associated with an increase in pH results in improved nerve penetration and more rapid onset time of nerve blockade (7,10).

Present knowledge of the action of the local anesthetic can best be characterized by the Hille unitary hypothesis (11). This indicates that local anesthetic activity is dependent on nerve membrane penetration by the nonionized local anesthetic. After penetration the nonionized drug disassociates into ionized and nonionized forms. The quantity of each varies with the pH of the axoplasm. The actual blockade of the sodium channel is felt to occur on the axoplasmic side of the nerve membrane with the ionized form of the local anesthetic attaching to a receptor within the sodium channel, with resultant blockade of nerve conduction. The first clinical report of shortened onset time for local anesthesia by increasing the pH of the anesthetic solution was by Gros in 1910 (12,13). A recent clinical report demonstrated that the addition of sodium bicarbonate to local anesthetic solutions resulted in a physiologic pH (pH 7.0–7.4). This addition was associated with a marked shortening of the analgesia onset time and prolongation of analgesic action (5). These effects stimulated the present clinical

study of pH-dependency of local anesthetic activity.

Shortening of the analgesia onset time also occurs when a carbonated solution is prepared by the addition of carbon dioxide to lidocaine solutions (14,15). In clinical reports the spread of analgesia appears to be more extensive when using carbonated lidocaine solutions, and the blockade of nerve fibers appears to be of better quality (16–18). These observations associated with the use of the carbonated lidocaine have been ascribed to three possible effects of carbon dioxide addition (19–21): 1) a direct depressant effect of the carbon dioxide itself on neural transmission; 2) an increase in the fraction of local anesthetic in the nerve axoplasm related to lowering of axoplasm pH caused by CO_2 transfer; and 3) an increased local anesthetic concentration in the axoplasm secondary to diffusion trapping with a lower intracellular pH. A further contributing explanation is suggested by our present study and a previous study (18). Solutions of carbonated lidocaine commercially available have a pH adjusted to 6.35-6.9 and the P_{CO_2} is 700 mm Hg. As CO_2 is lost on opening the vial, the pH of the solution should increase to above pH 7 (18). This represents an increase in pH from that of the standard commercial lidocaine with epinephrine solution (pH 4.35) or the plain lidocaine with freshly added epinephrine (pH 6.35). From our study, a further likely explanation of the altered onset characteristics seen with the use of carbonated lidocaine is the differences in the pH of the local anesthetics used.

The present study also found that onset of analgesia was significantly more rapid when epinephrine was added to plain lidocaine solution at the time of use of the drug compared to commercial preparations of lidocaine with epinephrine. The pH of the resultant

lidocaine solution was 6.3, in contrast to the standard shelf package of lidocaine with epinephrine with a pH of 4.35. This practice has been in use by many clinicians for a number of years. However, onset time using this solution (group 5 in this study) is less rapid than when bicarbonate is added to adjust the pH of a local anesthetic solution closer to the physiologic range. A similar observation was recently reported by Hilgier in which axillary nerve blocks using bupivacaine were more rapid in onset and had a longer duration if the solution was alkalinized with bicarbonate prior to use (22). The pH-adjusted bupivacaine had a pH of 6.4 compared to a pH of 3.9 in the commercial preparation used in the comparative group.

Another byproduct of this study is the demonstration that lidocaine blood levels are similar in patients receiving either pH-adjusted solutions (by adding bicarbonate) or non-pH-adjusted solutions. Theoretically, one might postulate that increased vascular penetration and systemic absorption occurs by increasing the pH of the local anesthetic solution (freebase concentration) at the site of injection. If this were to occur, increased local anesthetic toxicity secondary to higher blood levels might ensue. Higher blood concentrations have been reported with the use of carbonated salts of local anesthetics (23,24). However, in our present study this was not the case. Maternal and neonatal blood levels in patients having cesarean sections who received the pH-adjusted local anesthetic solutions were not significantly different from the plasma levels achieved using commercial preparations with low pH levels (Fig. 3).

The findings of this study demonstrate the desirable characteristics of epidural local anesthetic solutions where the pH has been adjusted towards the physiologic range with more rapid onset of both analgesia and surgical anesthesia. Also, the more rapid spread of the local anesthetic in the epidural space after pH adjustment is significant in that it allows for very early identification of adequate levels of anesthesia. Although it is true that final levels achieved with the local anesthetics at 30 min are independent of the pH adjustment, the rapidity of onset of adequate surgical anesthesia with pH adjustment suggests that this is a superior form of administration of local anesthesia that should be widely adopted.

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Hemodynamic Responses to Alfentanil in Halothane-Anesthetized Dogs

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KIEN ND, REITAN JA, WHITE DA, WU C-H, EISELE JH Jr. Hemodynamic responses to alfentanil in halothane-anesthetized dogs. Anesth Analg 1986;65:765–70.

Alfentanil is an opioid that has been used both as a sole anesthetic and in conjunction with other inhalation anesthetics. However, its effects on myocardial performance and regional blood flow are not clearly known. Using sonomicrometry and radioactive microsphere techniques, we examined the hemodynamic responses to alfentanil when given as a loading dose (45 $\mu g/kg$) followed by continuous infusion (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in dogs anesthetized with halothane. Similar plasma levels of alfentanil were observed after the loading and infusion doses, and both techniques of administration produced a significant reduction in arterial pressure without change in global or regional function of the left ventricle. Although cardiac output and left ventricular end-diastolic pressure remained unchanged, heart rate and systemic vascular resistance decreased significantly after the loading dose and recovered slightly when alfentanil was infused continuously. Despite the systemic hypotension, alfentanil did not alter perfusion to the heart, brain, muscle, and skin; however, blood flow to the renal cortex and the arterial supply to the liver decreased by 25 and 60%, respectively. Reduction in blood flow to the kidneys and the liver suggests that alfentanil should be used with caution when normal function of these organs is in question.

Key Words: ANESTHETICS, INTRAVENOUS—alfentanil. ANALGESICS—alfentanil. HEART, CARDIAC OUTPUT—distribution.

When used alone or as an anesthetic supplement, narcotic analgesic drugs adequately attenuate the systemic responses to surgical stress, with little cardiovascular perturbation. Because narcotic anesthesia is often associated with persistent respiratory depression during the postoperative period, considerable interest has focused on potent narcotics with rapid onset of action and rapid elimination. Alfentanil, a new opioid analgesic, is one-fourth as potent as fentanyl and has one-third the duration of action (1,2). Because of its rapid onset and short duration of action, alfentanil has been used both to induce anesthesia (3,4) and to maintain anesthesia during short surgical procedures (5–8). Even in large doses, alfentanil maintains cardiovascular stability in both animals (2) and humans (9). In cardiac patients, continuous infusion of alfentanil produces surgical anesthesia with little or no change in cardiovascular dynamics (10–12) and allows rapid recovery from anesthesia (10). When given as a supplement to inhalational anesthetics, narcotics enhance analgesia and reduce cardiovascular depression by lowering the MAC of inhalation agents (13,14). In the rat, halothane MAC is reduced by 48% with the infusion of 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ alfentanil (15).

Because most cardiovascular studies of alfentanil have concentrated on systemic responses (2,16–18), information on the influence of alfentanil on myocardial function and regional organ blood flow is scarce. In this study we used sonomicrometry and radioactive microsphere techniques to examine global and regional myocardial function, as well as organ blood flow, after loading and maintenance doses of alfentanil in dogs under halothane anesthesia.

Methods

Eight mongrel dogs (20.5–23 kg) were anesthetized with thiamylal (15 mg/kg), intubated, and ventilated using a positive-pressure Harvard respirator. Anesthesia was maintained with 1.5% of halothane in oxygen during surgery for instrumentation. Blood gas tension was measured intermittently for maintenance of P_{CO_2} and acid-base balance within normal limits.

Rectal temperature was measured continuously and maintained at 37°C with heating pads. A rigid catheter was placed in the abdominal aorta via the left femoral artery for monitoring systemic arterial pressure and for collection of arterial blood samples. A balloon-tipped catheter was placed in the pulmonary artery, and cardiac output was measured from a cardiac output computer (Edwards Model No. 9520) using cold saline as the indicator. Intravenous access was made available via a catheter in the cephalic vein. A thoracotomy was performed through an incision in the left fifth intercostal space. A sidehole catheter was inserted into the left atrial appendage for injection of radioactive microspheres. Left ventricular pressure was measured from a high-fidelity micromanometer (Konigsberg, P-7) implanted into the apex of the left ventricle. Left ventricular end-diastolic pressure and dP/dt were derived from the left ventricular pressure tracing. Pulse-transit ultrasonic dimension transducers were implanted in three pairs, the first onto the epicardium across the anterior–posterior minor axis to measure the transverse external diameter, the second into the anterior lateral free wall to measure the segmental length in the plane of the minor axis, and the third on the epicardium and opposite endocardium of the lateral wall for measurement of wall thickness. A high-frequency oscilloscope (Hewlett–Packard, 1200 AR) was used to confirm the proper alignment of the dimension transducers. Myocardial motions were monitored with a multichannel sonomicrometer (Triton Technology, 120). Inflatable balloon occluders were placed around both vena cavae for preload alteration during assessment of left ventricular contractility. Hemodynamic data and ventricular dimensions were recorded on a direct-writing recorder (Gould, 2800S) and on F-M magnetic tape (Ampex, SP300) for subsequent analysis.

Regional blood flow was determined using plastic microspheres, 15 μm in diameter, labeled with one of the three different isotopes Cr^{51}, Ce^{141}, and Sr^{85} (3M, Minneapolis, MN). The spheres, suspended in 10% dextran and 0.01% of Tween-80, were vigorously agitated using mechanical and ultrasonic mixers prior to injection into the left atrium. For each flow measurement, between 2 and 3×10^6 spheres in 0.5 ml aliquots were injected over 20 sec and flushed with 3 ml of warm saline. Reference blood was withdrawn starting 15 sec prior to the sphere injection and continued for 2 min at a constant flow rate of 7.75 ml/min.

After completion of instrumentation, the end-tidal halothane concentration was reduced to 0.75% (MAC 1). When cardiovascular measurements had stabilized and arterial blood gas tensions were normal, alfentanil was administered as a loading dose at 45 μg/kg

over 30 sec and followed 10 min later by an infusion of 3 μg·kg^{-1}·min^{-1}, using a variable speed Harvard infusion pump. Hemodynamic and blood flow measurements were made prior to alfentanil administration, 5 min after the loading dose, and 15 min after onset of infusion.

At the conclusion of the experiment, the animals were sacrificed by a combination of halothane overdose and intravenous saturated KCl. Organ tissues were then sampled, weighed, and their radioactive levels determined using a multichannel pulse height analyzer (Searle, Des Plaines, IL).

Calculations

Regional blood flow (RBF) was calculated in ml·min^{-1}·100g^{-1} tissue utilizing the formula RBF = $100 \times Ct \times \dot{Q}r/Cr \times Wt$, where Ct and Cr are radioactive counts of tissue sample and reference blood, respectively, and $\dot{Q}r$ and Wt are reference flow rate and tissue sample weight. Radioactive counts of tissue samples were corrected for energy overlap among the isotopes using stripping formulae.

Global ventricular function was assessed during transient vena caval occlusion with the respirator momentarily turned off. Fifteen consecutive heartbeats with no apparent arrhythmia were analyzed at end-systole. The left ventricular end-systolic pressure-diameter relationship was evaluated using linear regression analysis: $P = E_{es} (D - D_D)$, where P and D are left ventricular end-systolic pressure and diameter, respectively. D_D is the intercept of the diameter axis. E_{es} is the slope of the end-systolic pressure–diameter relation. Global ventricular function, measured using this slope, has been found to be closely related to the inotropic state of the heart and relatively independent of preload, afterload, and heart rate (19–21). Regional function of the left ventricular myocardium was evaluated from systolic shortening (%SS) of the diameter and the segmental length and systolic thickening (%ST) of the wall. The dimension changes that occurred during systole were expressed as percent of end-diastolic dimension.

Plasma concentrations of alfentanil were measured by radioimmunoassay using antibody and tracer obtained from Janssen Pharmaceutica, Beerse, Belgium. All samples were assayed in duplicate.

Statistical analysis of data included an analysis of variance and Student's t-test for paired data. All results were summarized as mean ± SEM and a probability value of less than 0.05 was considered statistically significant.
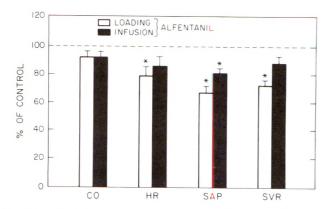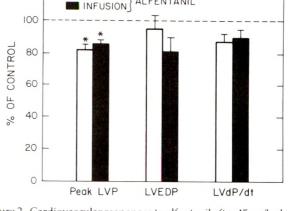
Figure 1. Cardiovascular response to alfentanil after 45 μg/kg loading dose and infusion of 3 μg·kg^{-1}·min^{-1}. Abbreviations: CO, cardiac output; HR, heart rate; SAP, systemic arterial pressure; SVR, systemic vascular resistance expressed as percent of control. Each bar represents the mean ± SEM of eight dogs. *P < .05 compared to control.

Figure 2. Cardiovascular responses to alfentanil after 45 μg/kg loading dose and 3 μg·kg^{-1}·min^{-1} infusion dose. Abbreviations: Peak LVP, peak left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; LVdP/dt, first time-derivative of left ventricular pressure tracing expressed as percent of control. Each bar represents the mean ± SEM of eight dogs. *P < .05 compared to control.

Results

Changes in cardiovascular variables after alfentanil administration are expressed in percent of control, as shown in Figures 1 and 2. Systemic arterial pressure decreased by 30% 5 min after the loading dose and by 21% 15 min into the infusion dose of alfentanil. No significant changes in heart rate and cardiac output were observed, whereas systemic vascular resistance decreased significantly from 2463 ± 159 to 1784 ± 142 dynes·sec·cm^{-5} after the loading dose and then increased to 2173 ± 190 dynes·sec·cm^{-5} during the infusion dose. The difference in systemic vascular resistance between loading and infusion doses was, however, not statistically significant. As shown in Figure 2, alfentanil decreased left ventricular peak pressure by 17.3 and 13.2% after the loading and infusion doses, respectively. There were no significant changes in left ventricular end-diastolic pressure and LVdP/dt.

Table 1 shows the effects of alfentanil on both global and regional function of the left ventricle. The slope (E_{es}) of the left ventricular end-systolic pressure–diameter relation decreased slightly after the loading dose and remained stable throughout the infusion. Neither the minor axis diameter of the left ventricle measured at end-diastole, nor the percentage of systolic shortening of this dimension, varied with alfentanil. Similarly, regional function, measured from end-diastolic segmental length and wall thickness and their percent systolic changes, was well-maintained after alfentanil administration.

Table 2 shows data for blood flow to various myocardial regions and organ tissues. Alfentanil did not alter blood flow to either the brain or the heart. Muscle and skin blood flow also remained unchanged after alfentanil. However, renal cortical and hepatic arterial blood flows decreased by 25% and 60% respectively.

Plasma concentration of alfentanil was 29.8 ± 5.15 ng/ml 5 min after the loading dose. Blood samples taken at 5, 10, and 15 min after the onset of infusion indicated that the plasma concentration of alfentanil reached a plateau of approximately 30 ng/ml (Table 3).

Discussion

Alfentanil produced a statistically significant decrease in systemic arterial pressure when given as a single bolus dose followed by continuous infusion in halothane-anesthetized dogs. The reduction in blood pressure appeared to be greater after the loading dose of alfentanil; however, blood pressure after the loading dose was not statistically different from the pressure during continuous infusion of alfentanil (Fig. 1). The similar reduction in blood pressure may be explained by the similar levels of plasma alfentanil after the two doses. Similar effects of alfentanil on blood pressure have been reported both in humans (9,10) and in dogs (16). In our laboratory, vascular resistance decreased significantly when alfentanil was administered in an isolated and denervated hind-limb preparation (unpublished data), which indicated that alfentanil exerted a vasodilatory effect directly on the peripheral vasculature. Conversely, in a conscious dog model, a substantial increase in blood pressure after alfentanil injection has been reported (18). Because the influence of opioids on cardiovascular function is

Table 1. Global and Regional Function of the
Left Ventricle

| | Control | Alfentanil | |
		Loading	Infusion
Global			
E_{es} (mm Hg/mm)	10.6 ± 1.4	9.3 ± 1.1	9.2 ± 1.0
Minor axis (mm)	59.3 ± 1.6	59.0 ± 1.5	59.7 ± 1.6
% SS	7.7 ± 0.5	8.3 ± 0.5	7.5 ± 0.6
Regional			
Segmental length (mm)	10.6 ± 0.8	10.5 ± 0.9	10.6 ± 0.8
% SS	9.7 ± 1.4	10.2 ± 2.0	8.4 ± 1.5
Wall thickness (mm)	12.3 ± 0.8	12.2 ± 0.9	12.4 ± 0.8
% Wall thickening	14.4 ± 1.4	16.4 ± 2.1	15.2 ± 1.6

Values are expressed as mean ± SEM.
Abbreviations: E_{es}, the slope of the end-systolic pressure–diameter relation; %SS, systolic shortening of diameter and segmental length.

Table 2. Regional Blood Flow (ml·min^{-1}·100 g^{-1})

| | Control | Alfentanil | |
		Bolus	Infusion
Myocardium			
Atrium	87.7 ± 7.0	79.6 ± 9.7	85.7 ± 11.0
Ventricular septum	90.6 ± 9.7	77.1 ± 13.8	88.3 ± 15.4
Right ventricle	71.7 ± 7.2	61.7 ± 10.8	68.7 ± 12.0
Left ventricle			
endo	99.6 ± 6.7	82.8 ± 15.1	83.5 ± 12.2
epi	97.6 ± 7.0	76.4 ± 14.6	83.2 ± 10.8
Endo/epi	1.04 ± 0.05	1.09 ± 0.08	1.00 ± 0.03
Cerebral cortex	48.6 ± 4.7	42.1 ± 5.2	47.5 ± 3.4
Hepatic arterial flow	33.8 ± 5.6	17.7 ± 3.3[a]	13.6 ± 2.0[a]
Renal cortex	607.6 ± 37.8	475.7 ± 53.5[a]	457.4 ± 35.5[a]
Muscle	5.0 ± 1.5	5.5 ± 1.8	4.9 ± 2.1
Skin	2.2 ± 0.8	1.9 ± 0.8	2.6 ± 1.2

Values are expressed as mean ± SEM.
[a] $P < 0.05$ compared to control.

Table 3. Alfentanil Plasma Concentrations

Time of sample	Alfentanil concentrations (ng/ml)
Min after loading dose	
5	29.80 ± 5.15
10 (start of infusion)	14.06 ± 1.56
Min into infusion	
5	26.66 ± 4.71
10	30.46 ± 5.55
15	29.88 ± 4.72

Values are expressed as mean ± SEM.

nificant changes were observed in either regional or global function of the left ventricle, whereas in conscious dogs in other investigations, substantially larger doses of alfentanil (160–200 µg/kg) increased cardiac contractility as measured by E_{es} (17) and by LVdP/dt max and LVdP/dt max/P (2). The inconsistency in these findings may be due to the different drug doses and to the basal halothane anesthesia employed in our experiment, which may have attenuated a positive inotropic effect of alfentanil. Myocardial contractility and preload measured by end-diastolic pressure and diameter did not change after alfentanil. Apparently cardiac output was maintained in the presence of the bradycardia by an increase in stroke volume as a result of afterload reduction.

The maintenance of blood flow to the cerebral cortex and various myocardial regions indicates that the vascular autoregulatory mechanisms of the brain and the heart were well-preserved during alfentanil and halothane anesthesia. Because both regional and global performances of the left ventricle are quantitatively related to the sufficiency of myocardial perfusion (25), it is believed that adequate blood flow was responsible for sustaining normal myocardial function observed in this study.

In dogs, renal blood flow is little altered from the awake value during one MAC halothane anesthesia (23,26); however, total hepatic perfusion has been shown to decrease in a dose-dependent fashion at halothane concentrations varying from 0.7 to 2.7 MAC (27,28). Even though visceral blood flow depends directly upon the systemic perfusion pressure (29), targeted organs may respond differently to certain pharmacologic agents. In our study, the decrease in renal perfusion was closely related to the alfentanil-induced decrease in systemic arterial pressure, suggesting that renal autoregulation had been attenuated by the opioid-halothane combination (3).

The decrease in arterial blood flow to the liver, on the other hand, exceeded the decrease in arterial flow to the kidney more than two-fold after alfentanil administration. Because the radioactive microsphere

related to the level of circulating plasma catecholamines (22), it is most likely that the vascular effect of alfentanil also depends upon existing sympathetic tone. Therefore, the hypotensive effect of alfentanil in our study may be a result of combined direct vasodilation and sympathetic suppression. Because halothane is known to reduce blood pressure and left ventricular function (23), the observed hypotension in this study may be the result of an interaction between halothane and alfentanil. The bradycardia observed with alfentanil is a typical effect of opioids on heart rate. This negative chronotropic action is believed to originate from the central nervous system, mediated via the vagus nerve (24).

Despite the reductions in blood pressure and heart rate, left ventricular dynamics were well-maintained after alfentanil administration. In our study, no sig-

technique is limited to assessment of the arterial perfusion of an organ (31), blood flow to the liver in our study only accounts for measurement of the hepatic arterial portion and does not include the portal venous inflow (32). In the normal liver, approximately one-third of the total hepatic flow comes from the arterial source, which supplies about 50% of the metabolic oxygen (33,34). Ligation of the hepatic artery can generally be done with impunity because of the compensatory flow from the portal vein (34,35). However, in a diseased or compromised organ, a significant reduction in arterial perfusion and the subsequent loss of nutrients may have a profound effect. Indeed, experience in liver transplantation has shown that interruption of the arterial supply caused by thrombosis invariably leads to organ failure (36). It is difficult to postulate that a 60% decrease in arterial perfusion to a normal, healthy liver may be clinically detrimental; but in an organ in shock (34), or significantly debilitated from hepatic disease, particularly cirrhosis, such a loss of oxygen source may be deleterious. This is an area that requires further investigation.

The mechanism by which alfentanil decreases hepatic arterial flow is unknown. However, it is postulated that the excessive reduction in arterial flow to the liver, observed in this study, may be the consequence of the reciprocal mechanism of the hepatic vasculature, which causes vasoconstriction in the hepatic artery in response to an increase in portal venous blood (37).

In conclusion, loading and supplemental doses of alfentanil in halothane-anesthetized dogs produced significant hypotension without disturbances in myocardial performance or blood flow. While blood flows to the brain and carcass were maintained, blood flows to the kidney and to the liver via the hepatic artery decreased significantly. Whether the reduction in blood flows observed in this study occurs in humans or in other animal models is not known; also unclear is the influence of blood flow reduction on the distribution and elimination of alfentanil, particularly when normal function of the kidney and the liver is in doubt. Further research is warranted to address these questions.

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Electrical and Mechanical Train-of-Four Responses during Depolarizing and Nondepolarizing Neuromuscular Blockade

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WEBER S, MURAVCHICK S. Electrical and mechanical train-of-four responses during depolarizing and nondepolarizing neuromuscular blockade. Anesth Analg 1986;65:771–6.

Simultaneous measurements of train-of-four (TOF) responses by integrated electromyography (IEMG) and twitch force were compared for atracurium, vecuronium, and succinylcholine in 30 subjects during nitrous oxide–fentanyl anesthesia. Determinations of TOF were made during neuromuscular blockade (NMB) onset and recovery. Scattergrams and least squares regression lines were plotted, and z-tests for parallel slope and common intercept were used to compare lines. Data for atracurium and vecuronium were indistinguishable in all groups (z < 0.05), and therefore pooled to represent nondepolarizing blockade. During onset of nondepolarizing NMB, TOF showed a linear relationship indistinguishable from the line of identity (slope 0.93, intercept −0.06, z < 0.05). During recovery the intercept was unchanged (z > 0.05), but the slope was significantly changed, indicating mechanical TOF lags behind IEMG during recovery. This finding is important for interpretation of IEMG when used for clinical monitoring. Comparison of data for depolarizing NMB shows more complex relationships. Integrated electromyography is found to be convenient and reliable for monitoring nondepolarizing NMB.

Key Words: MEASUREMENT TECHNIQUES—electromyography. MONITORING—neuromuscular function. NEUROMUSCULAR RELAXANTS—atracurium, vecuronium, succinylcholine.

Monitoring of neuromuscular blockade is an essential but still evolving component of anesthetic management. The use of electromyography (EMG) for this purpose was first described in 1952 (1); however, because of its complexity and high cost it was eclipsed in the clinical setting by simple measurements of force of neurally evoked muscle twitch (mechanomyography, MMG). Recent improvements in complex electrical signal processing may change this situation. Electromyography correlation with MMG-evoked single twitch response during both depolarizating and nondepolarizing neuromuscular blockade (NMB) is known (2–5), but the relationship of EMG and MMG responses to train-of-four stimulation have been reported only during anesthesia with halothane (6). Halothane has direct effects on excitation–contraction coupling and may itself modify evoked responses. We used a newly developed, commercially available nerve stimulator and electromyography unit (Puritan-Bennett NMT 221) to compare integrated EMG (IEMG) to corresponding MMG responses for train-of-four (TOF) stimulation. Comparisons were done both during onset of and recovery from depolarizing and nondepolarizing NMB, in patients undergoing nitrous oxide–fentanyl anesthesia.

Methods

Thirty adult surgical patients (ASA class I–III, aged 17–87) participated in the study protocol after approval by the local Committee on Studies Involving Human Beings. No patients had known neuromuscular disorders, trauma, or pseudocholinesterase deficiency. They received either intramuscular morphine and an antisialogogue, or diazepam, or no premedication. In addition to routine monitoring, patients had one arm immobilized in a splint equipped with a strain-gauge force transducer. This transducer was coupled to the thumb with a preload tension of 100–300 g, in a manner consistant with all previously described specifications for measurement of evoked force of the adductor pollicis muscle (7–9). Electrical activity over the hypothenar aspect of the hand (see Discussion) was monitored with silver–silver chloride surface electrodes, and the signal was amplified, fil-

tered, rectified, and then electronically integrated to provide digital display of the IEMG T4/T1 ratio as well as the T1 (first twitch of the TOF) expressed as a percentage of the control value obtained prior to use of relaxants. All responses were continously recorded.

Anesthetic induction was carried out with thiopental, 3–5 mg/kg, and fentanyl, 6–8 μg/kg intravenously. Anesthesia was maintained with 60–70% nitrous oxide in oxygen, and additional small doses of thiopental and fentanyl. No potent inhalation anesthetics were used. Immediately after loss of consciousness, train-of-four confirmed supramaximal (range 45–50 mA) 0.1-msec duration square wave impulses were delivered over the ulnar nerve in 2 sec (0.5 Hz) every 20 sec. Patients then received either atracurium (0.4 mg/kg total body weight), vecuronium (0.08 mg/kg), or succinylcholine (1 mg/kg) by intravenous infusion over 2–3 min followed by additional slow infusion as required to maintain clinically adequate NMB (MMG less than 50% of control). Three determinations of simultaneous MMG and IEMG T1 and T4/T1 were made during onset of NMB (initial period of increasing NMB) and then again during recovery (spontaneous lessening of NMB). No determinations were made during periods of rapid changes in infusion rate or after the administration of reversal drugs.

The simultaneous MMG and IEMG T1 and T4/T1 values produced by each relaxant during onset and recovery were plotted on scattergrams. Linear regression lines (least-squares method) were compared using large sample z-tests for parallel slope and common intercept, $z < 0.05$ the criterion of significance (10). Correlation coefficients were calculated for each scattergram. Mean values for demographic data were compared with two-tailed t-tests, with $P < 0.05$ the criterion of statistical significance.

Results

During onset of NMB, the slopes and intercepts derived from linear regression lines of IEMG vs MMG T4/T1 data for the ten patients receiving atracurium and for the ten receiving vecuronium infusions (slopes 0.78 and 1.03, intercepts 4.8 and −4.6, respectively) were statistically indistinguishable. These data were pooled into a single group to represent the response of these twenty patients to nondepolarizing NMB. During onset, MMG vs IEMG T4/T1 demonstrated a linear relationship that was not statistically distinguishable from identity (Fig. 1A). During recovery from nondepolarizing NMB (Fig. 1B), a linear relationship was maintained, intercept was unchanged, but slope was significantly reduced ($z < 0.05$). During
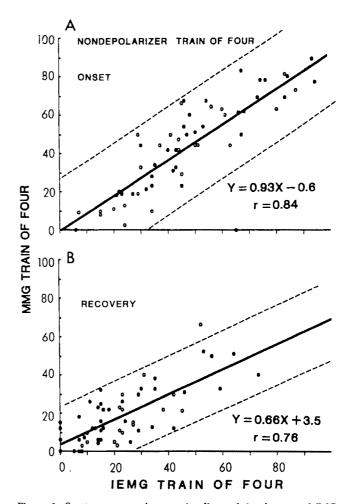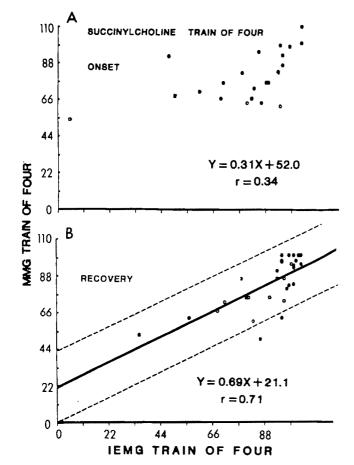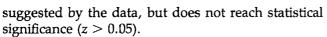
Figure 1. Scattergrams and regression lines of simultaneous MMG vs IEMG T4/T1 data points during nondepolarizing neuromuscular blockade. (A) Onset phase of NMB. (B) Recovery phase of NMB. Dashed lines represent 95% confidence interval for data points around the regression lines; r is the correlation coefficient.

onset of succinylcholine-induced depolarizing NMB (Fig. 2A), no significant relationship between IEMG and MMG TOF responses could be demonstrated for the ten patients receiving this drug. However, during recovery, a linear relationship with a slope less than 1.0 ($z < 0.05$), and intercept greater than zero ($z < 0.05$) did appear (Fig. 2B).

Comparison of MMG and IEMG first twitch response (T1 as percent of control) revealed a linear correlation during both onset and recovery from depolarizing NMB (Fig. 3A and 3B). Neither slopes nor intercepts differed significantly between the onset and recovery periods ($z < 0.05$). First twitch data from patients receiving atracurium or vecuronium were again indistinguishable for both slope and intercept, and like T4/T1 data, were pooled to yield single relationships between MMG and IEMG during onset of and recovery from nondepolarizing NMB (Fig. 4A and 4B). A difference in slope between onset and recovery is
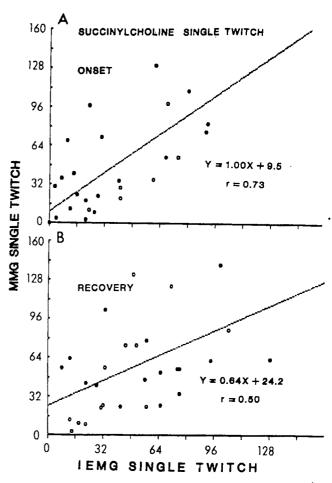
Figure 2. Scattergrams and regression lines of simultaneous MMG vs IEMG T4/T1 data points during succinylcholine neuromuscular blockade. (A) Onset phase of NMB. (B) Recovery phase of NMB.

Figure 3. Scattergrams and regression lines of simultaneous MMG vs IEMG T1 (first twitch) data points during succinylcholine neuromuscular blockade. (A) Onset phase of NMB. (B) Recovery phase of NMB.

suggested by the data, but does not reach statistical significance ($z > 0.05$).

Comparison of age, weight, electrical current required for supramaximal stimulation, force transducer preload, body temperature, and ventilatory status (Table 1) revealed no significant differences between the three groups studied.

Discussion

Although clinical monitoring of NMB by subjective evaluation of gross visual response to nerve stimulation is known to be limited in value (11,12), quantitative techniques such as EMG and MMG are not widely used because they are expensive and inconvenient. The development of integrated EMG (IEMG) may reduce these problems. However, it is not fully proven that IEMG responses during NMB are equivalent to MMG measures of single twitch and TOF T4/T1 ratio. These MMG measures are the standards

on which clinical neuromuscular blockade monitoring is based.

Because of the heretofore limited use of EMG for NMB monitoring, standardized clinical techniques have yet to be established, including standards for location of EMG recording electrodes. Previous investigators considered data obtained with electrode placement over the thenar or hypothenar aspects of the hand to be acceptable (4,13). In the present investigation, as in Kopman's work on IEMG measurement of TOF (6), EMG recording electrodes were placed over the hypothenar muscles. This location is advantageous because: 1) it is less subject to movement artifact caused by twitch-related movement of the hand; and 2) the hypothenar muscles are more superficial than the thenar muscles, minimizing the amount of tissue between muscles and recording electrodes and reducing the likelihood of measurement artifact.

The selection of hypothenar lead placement raises a question concerning the comparisons made in this
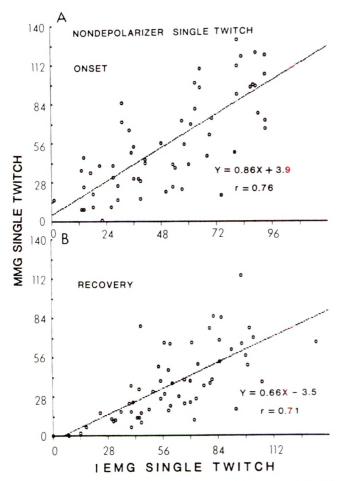
Figure 4. Scattergrams and regression lines of simultaneous MMG vs IEMG T1 (first twitch) data points during nondepolarizing neuromuscular blockade. (**A**) Onset phase of NMB. (**B**) Recovery phase of NMB.

study. It is known that different muscles respond differently to neuromuscular relaxants, and this could theoretically affect the validity of comparisons made between adductor pollicis MMG and hypothenar IEMG. However, no data exist to indicate that the physiologic differences between thenar and hypothenar muscles in humans affect clinical monitoring of NMB. The major physiologic differences found between muscle types correspond to a large extent to the relative ratios of fast to slow muscle fibers found in the muscles. Most muscles are mixtures of these fibers (generally ranging from 30–90% slow fibers) (14). The human adductor pollicis muscle contains approximately 80% slow fibers, and the abductor digiti minimi (a major component of the hypothenar muscles) contains about 52% slow fibers (14). More study is needed to clarify the clinical significance of differences of this magnitude, and further speculation on this question is beyond the scope of this investigation.

The only study addressing this issue in humans was done by Katz (3), who looked at tetanic fade (a measure closely related to T4/T1) at various levels of d-tubocurarine-induced NMB. He found thenar and hypothenar EMG responses to indirect electrical nerve stimulation to be similar to each other, as well as similar in magnitude to mechanical responses of the adductor pollicis muscle, and found no statistically significant differences between any of these groups. His study involved only six patients, indicating the need for further work to clarify the relationships of thenar and hypothenar EMG measurements of TOF. For single twitch EMG monitoring, Katz found the hypothenar twitch response to be slightly less depressed by d-tubocurarine than the thenar twitch response. Both of these responses were greater than the adductor pollicis MMG response. The results we obtained for vecuronium and atracurium single twitch response are similar to those previously obtained by Katz. The observations on TOF reported here are the first to be obtained in the absence of volatile anesthetics and the first to examine correlations between IEMG and MMG during onset as well as during recovery from NMB. The data show internally consistent significant differences for various IEMG–MMG TOF correlations, and therefore provide new information concerning the relationships between IEMG and MMG.

As noted above, previous studies have compared the relationship between EMG and MMG during halothane anesthesia. Epstein and Epstein (15) measured single twitch after small (0.1 mg/kg) doses of d-tubocurarine during halothane anesthesia and found that MMG depression exceeded EMG depression. Fisher and Miller (16) used a dual EMG–MMG apparatus to quantitate vecuronium NMB under halothane anesthesia; they also found greater MMG than EMG depression in most cases. Similarly, Kopman found that during halothane anesthesia, atracurium MMG depression of T4/T1 exceeds IEMG depression (6). Because mechanical and electrical evoked responses represent different but closely related physiologic events occurring in response to nerve stimulation, the differences in NMB measurement under these circumstances could be due to a specific effect of halothane (and possibly other potent inhalational agents) upon evoked mechanical response. Changes in skeletal muscle contractile state are not discernible using EMG monitoring techniques: EMG measures only electrical responses of the muscle endplate and sarcolemma to cholinergic transmission (17). Our results are in agreement with a similar, earlier report by Katz (2) who found that IEMG and MMG T4/T1 and T1 are virtually equivalent measurements of evoked

Table 1. Patient Characteristics and Clinical Data

Relaxant[a]	Age (yr)	Weight (kg)	Dose (mg)	Supramaximal stimulation (mA)	Preload (g)	Onset temperature (°C)	Final temperature (°C)	Onset ETCO₂ (torr)	Final ETCO₂ (torr)
Atracurium	42.3 ± 5.6	63.4 ± 3.1	37.3 ± 7.4	47.2 ± 1.2	170.0 ± 12.4	35.8 ± 0.4	35.8 ± 0.3	32.5 ± 1.3	35.4 ± 0.4
Vecuronium	51.3 ± 4.0	62.2 ± 1.5	5.7 ± 0.8	46.5 ± 1.1	186.0 ± 32.9	36.3 ± 0.3	35.5 ± 0.4	36.0 ± 4.3	38.8 ± 4.9
Succinylcholine	33.5 ± 10.6	69.8 ± 4.7	98.2 ± 28.8	48.0 ± 1.3	112.5 ± 26.8	36.5 ± 0.2	35.0 ± 0.2	38.0 ± 1.6	38.0 ± 2.4

All data are mean ± SE.
[a]There were no statistically significant differences among the muscle relaxant subgroups.

response during the early phases of nitrous oxide–narcotic anesthesia if potent inhalational anesthetics are avoided.

During spontaneous recovery from nondepolarizing NMB during nitrous oxide–narcotic anesthesia (Fig. 1B), we observed a significant flattening of the MMG–IEMG relationship, similar to that reported previously with halothane (6,15,16). A number of explanations may be plausible. Over time, nitrous oxide may selectively depress the mechanical properties of skeletal muscle without having comparable effects on the electrical properties of such muscle. However, we observed that the slope of the lines comparing IEMG and MMG for T4/T1 (an indication of neuromuscular transmission fade) and for T1 (an indication of neuromuscular transmission amplitude) were both depressed to a roughly equal extent. The similarity of this effect on these different aspects of neuromuscular transmission suggests that an isolated effect on muscle contractile properties is unlikely. Alternatively, it is possible that the change in the slope of the relationship may reflect a progressive, time-related change in the characteristics of evoked neuromuscular responses after establishment of NMB or continuing exposure to nitrous oxide or other agents. Such mechanisms could explain why previous studies that combined data from both onset and recovery phases found, as we did, a linear relationship between the two monitoring techniques, but with the slope less than identity.

Onset of depolarizing NMB after the use of succinylcholine produced a state in which no correlation between MMG and IEMG T4/T1 could be demonstrated. However, the MMG/IEMG T1 relationship showed a slope indistinguishable from identity, with a positive y-intercept (Fig. 3A). This second finding is consistent with the "augmentation" of mechanical evoked response previously noted under similar circumstances (5,18). There was also marked interpatient variability. During recovery from succinylcholine NMB, the positive y-intercept was maintained, and a significant linear relationship appeared for MMG vs IEMG T4/T1. The high T4/T1 values make it unlikely that "phase II" block occurred. This difference

in MMG/IEMG relationship between onset and recovery suggests that succinylcholine-induced NMB, like nondepolarizing NMB, may change in character over time.

The positive y-intercepts seen on all three of the significant depolarizing NMB MMG–IEMG relationships shown in the figures imply that a mechanical response is possible in the absence of evoked electrical response. Clearly, this is unacceptable on a physiologic basis. It is possible that with depolarization the artifact filtering mechanism of the NMT 221 eliminates all or part of the signal, resulting in artifactual low readings of evoked EMG responses. Alternatively, a differential effect of succinylcholine on different hand muscle groups might permit returning adductor pollicis function to go undetected by surface electrodes recording activity on the hypothenar aspect of the hand. Reevaluation of IEMG processing techniques and of the effect of lead placement may provide the data necessary to explain this phenomenon.

In summary, our results suggest that with nitrous oxide–narcotic anesthesia there is good correlation and general equivalence between IEMG and MMG measurements of both T1 and T4/T1 values after TOF stimulation during the onset phase of nondepolarizing NMB. Subsequent observations suggest that although these linear relationships are maintained during spontaneous recovery from NMB, mechanical responses lag behind EMG indices of recovery. Thus, during recovery from nitrous oxide–narcotic anesthesia, as during halothane anesthesia, full recovery of electrical aspects of neuromuscular transmission may occur although other factors continue to impair overall muscle strength and the ability to maintain repetitive stimulation, capacities indicated by MMG T1 and T4/T1, respectively.

Because an MMG T4/T1 ratio greater than 0.70 appears to correlate well with adequate clinical recovery from neuromuscular blockade (19), our data suggest that a comparable standard for patients in whom IEMG is used to monitor NMB would be closer to 100% recovery of T4/T1. In his study, Kopman found that at EMG T4/T1 values greater than 0.90, MMG T4/T1

values were predictably above 0.60 (6). Although we found a linear correlation between MMG and IEMG T1 during both onset and recovery from depolarizing NMB, the wide variability in the magnitude of "augmentation" of mechanical twitch makes clinical interpretation of this data more difficult.

We conclude that integrated electromyography is a convenient and reliable method for clinical monitoring of nondepolarizing neuromuscular blockade. It can be used to determine and document adequacy of blockade as well as return of neuromuscular function if the relationships described above are considered.

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Prevention of Silent Aspiration Due to Leaks around Cuffs of Endotracheal Tubes

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Significant aspiration may occur around correctly inflated high volume, low pressure endotracheal tube cuffs. The prevention of silent aspiration due to leaks around cuffs of endotracheal tubes was investigated during general anesthesia for hip replacement in 47 patients. The patients were randomly assigned to one of three groups, in which one of three endotracheal tubes of different designs were used for intubation. The following three tubes were used: the red rubber Rüsch tube with low residual volume cuff, inflated to minimum occluding volume; the Mallinckrodt Hi-Lo tube with high residual volume cuff; the NL tube with high residual volume cuff and automatic cuff pressure regulation. The cuffs on the Mallinckrodt and the NL tubes were inflated to 29-31 cm H_2O. One hour before termination of the surgical procedure, 1 ml methylene blue dye was injected into the trachea just above the cuff through a thin channel built into the tubes. At termination of the operation, the trachea below the cuff was inspected with a fiberoptic bronchoscope. Aspiration was found in 12.5% with the Rüsch tube, in 31.2% with the Mallinckrodt tube, and in 0% with the NL tube. Our resuts show that silent aspiration is still a problem with standard endotracheal tubes, but that it may be minimized by use of appropiate tubes, cuffs, and control of cuff inflation.

Key Words: EQUIPMENT, TUBES—tracheal. INTUBATION—tracheal. LUNG—aspiration.

The cuffs of endotracheal tubes are usually expected to prevent aspiration of gastric contents and pharyngeal secretions or blood into the lungs. However, significant aspiration has been reported using high volume cuffs (1,2).

The frequency of silent aspiration has been evaluated for patients undergoing general anesthesia (3) and for intensive care patients in studies in which dye solutions were placed in the pharynx (4–6). Aspiration was confirmed if dye was found in the trachea below the cuff, either by tracheal suction or by direct observation. However, a more reliable method for testing the ability of a cuff to prevent silent aspiration would be to place the dye solution just above the cuff and thereafter inspect the trachea below the cuff for staining before extubation. This is the method used in the present investigation designed to compare the frequency of silent aspiration of three different designs of endotracheal tubes during general anesthesia in patients undergoing identical surgical procedures.

Methods

The study was approved by the local ethical committee. Informed consent was obtained at the time of preoperative visit from 47 patients scheduled for elective hip replacement.

Two standard commercially available endotracheal tubes were studied: the red rubber Rüsch endotracheal tube with low residual volume latex cuff and the Hi-Lo Mallinckrodt tube with high residual volume PVC cuff. The third tube was the NL tube designed by Lomholt, based on his tracheostomy tube (7,8). The most important differences between the NL tube and the other more conventional tubes are the 35-mm, pear shaped, thin-walled polyurethane cuff and the rapid automatic correction of cuff pressure achieved with the NL Cuff Inflator (Dameca, Denmark). The Cuff Inflator contains a manometer and a precision reduction valve, which reduces the pressure
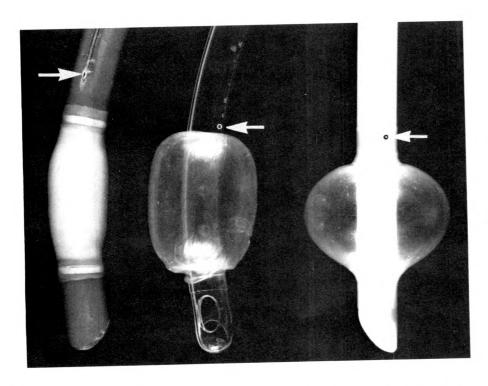
Figure 1.. The three tubes evaluated in this study with the arrows pointing at the end of the built-in injection channel. From left to right: the red rubber Rüsch with low residual volume latex cuff, the Mallinckrodt with high residual volume PVC cuff, and the NL with high residual volume polyurethane cuff.

of oxygen or air from a wall outlet to between 29 and 31 cm H_2O. By including a small leak in the system, cuff pressures both above and below 30 cm H_2O are corrected within fractions of a second (8). All the tubes used in our study were modified by addition of a thin channel (1.0 mm OD) built into the wall of the tubes ending just above the cuff.

To test in vivo whether the cuff occluded the trachea tightly, 1 ml of a methylene blue solution was injected through the channel approximately 1 hr before extubation (Fig. 1). The patients were assigned to three groups. For patients in group 1 ($n = 16$), Rüsch tubes were used; for patients in group 2 ($n = 16$), the Mallinckrodt tubes were used; for patients in group 3 ($n = 15$), the NL tubes were used. The cuffs were inflated according to conventional standards for each type of tube. The Rüsch tubes were inflated with minimum occluding volume, and the cuff pressure was not regulated during the anesthesia. The Mallinckrodt tubes were inflated with the NL Cuff Inflator to between 29 and 31 cm H_2O and maintained connected to the Cuff Inflator. After inflation, the cuff inflation tube was clamped. Every half hour the clamp was briefly removed in order to reduce the cuff pressure to 29–31 cm H_2O. The NL tubes were used with the cuff pressure maintained at 29–31 cm H_2O by permanent connection to the NL Cuff Inflator. Excluded from the study were patients who required more than one attempt at orotracheal intubation, patients who remained intubated after discharge from the operating room, patients who had a nasogastric

tube passed before or during the operation, and patients who complained of sore throat before anesthesia.

On the day of operation, after overnight fasting, patients were premedicated with meperidine, 75 mg intramuscularly (IM), half an hour before surgery. After injection of atropine, 1 mg intravenously (IV), and precurarization with pancuronium, 1 mg IV, general anesthesia was induced with thiopental, 4 mg/kg, followed by succinylcholine, 100 mg IV. All intubations were performed by an experienced anesthetist. All tubes were lubricated with lidocaine spray, 1%, and securely fixed to prevent any movement. Anesthesia was maintained with fentanyl–droperidol and N_2O. Muscle relaxation was maintained with pancuronium. The patients were ventilated with a MCM ventilator (Dameca, Denmark). The cuff pressure was maintained as described above, and no manipulation of the tubes occurred until extubation. The sizes of the tubes ranged from 7.0 to 8.0 ID.

After completion of the surgical procedure, the operating table was tilted 30° head-up, and a fiberoptic bronchoscope (Olympus BF type 3C4) was passed through the endotracheal tube to inspect for dye distal to the cuff. Photographs were taken using the SC 16-3 Olympus camera. The bronchoscopist was, of course, aware of which endotracheal tube had been used. However, the photographs were analyzed by an experienced bronchoscopist who was unaware of which tube had been used. The data were evaluated for statistical significance using χ^2-analysis and Goddman–Kruskal γ-analysis of variance.

Table 1. Patient Characteristics

	Rüsch tube	Mallinckrodt tube	NL tube
Female/male	14/2	12/4	13/2
Age (yr)	73 ± 1.2	73 ± 1.6	74 ± 1.9
Weight (kg)	70 ± 2.9	66 ± 2.9	64 ± 2.9
Number of previous general anesthetics	1.7 ± 0.5	2.1 ± 0.4	1.8 ± 0.3
Duration of intubation (min)	183 ± 8.8	200 ± 8.0	192 ± 10.6

Values are expressed either as number of patients or mean ± SEM.

Results

The duration of intubation, sex, and age distribution were similar in all groups of patients studied (Table 1). Leak around the cuff was detected in seven of the 47 patients. In the 16 patients in group 1 (in whom the Rüsch tube with low residual volume cuff was used) two patients (12.5%) had a positive methylene blue dye test for leak. In group 2 patients (in whom the Mallinckrodt tube with high residual volume cuff was used), five (31.2%) of the 16 tested positive. In group 3 (NL tube with high residual volume cuff) none of the 15 patients tested positive (0%).

The difference between the Mallinckrodt and the NL tube was statistically significant ($P = 0.004$). The difference between the Mallinckrodt group and the Rüsch group compared with the NL group was significant ($P = 0.002$), whereas the difference between the Mallinckrodt and the Rüsch group was not statistically significant.

Discussion

The magnitude of the problem of pulmonary aspiration from the pharynx that should be solved by a cuff attached to the endotracheal tube can be estimated from the experience with uncuffed tubes during general anesthesia. Weiss (9), Culver et al. (10), and Berson and Adriani (11) found that in 25–26% of their patients, regurgitation occurred, and when it did occur 56–76% showed evidence of aspiration.

The results from the present investigation showing cuff leakage in 12.5% of patients intubated with the Rüsch tube, in 31.2% with the Mallinckrodt tube, and in none using the NL tube, were unexpected, because the two high residual volume cuffs were believed to peform identically. It could be argued that the cuff pressure regulation was different, as the cuff pressure in the Mallinckrodt tube was only regulated every half hour, which is in accordance with clinical practice. This should decrease rather than increase the tendency for leakage to occur, because the pressure within the cuff between unclamping of the cuff, due to N_2O diffusion, would increase by about 50% (12). Our results are not in accordance with those of Bernhard et al. (3), who found that the Mallinckrodt Hi-Lo tube with a cuff pressure of 25 cm H_2O prevented aspiration. As the variation between groups 2 and 3 in our study cannot be explained by cuff pressure regulations procedures, the difference in cuff design is therefore the most probable explanation. The thickness of the Mallinckrodt cuff is 0.060 mm, whereas the polyurethane cuff on the NL tube is only 0.025 mm. The thinner the cuff, the sharper the foldings and the smaller the channels through which liquid may travel down the trachea. Polyurethane is more pliable and more rubberlike than PVC, and this improves its ability to occlude the trachea tightly. The fast pressure regulation with the NL Cuff Inflator (inflation within 0.1 sec) may also be important (8). Because the trachea is compliant, tracheal diameter changes with differences between intrathoracic and intratracheal pressures. A change in position or a deep inspiration may thus lower the pressure in a high residual volume cuff from 30 cm H_2O to 5 cm H_2O in the absence of methods used to regulate cuff pressure (unpublished results). Metha (13) investigated the maximum hydrostatic pressure on the cuff during regurgitation by measuring vertical and horizontal distance from the cuff to the incisors, and found a distance of 9 cm in the supine and of 21 cm in the vertical position. (Probably the pressure on the cuff may become even higher during explosive vomiting.) It was recommended to maintain an intracuff pressure between 25 and 30 cm H_2O. It has been argued that small diameter, high compliance cuffs filling the trachea without invaginations are preferred to high residual volume cuffs (1). Small diameter cuffs tend to center the tube in the trachea. The force that centers the tube in the trachea will, however, increase the cuff pressure on one side of the trachea and decrease the pressure on the opposite side, and consequently may facilitate aspiration. With adult tracheas of different shapes, a uniform pressure on the tracheal mucosa can be obtained only with a cuff diameter of at least 30 mm.

With high residual volume cuffs, it was found that 7.8% of 900 patients had silent aspiration during gen-

eral anesthesia (14), and 38.5% had silent aspiration with high residual volume Lanz and Mallinckrodt tubes if the cuff pressure was 20 cm H_2O. Aspiration was prevented with a cuff pressure of 25 cm H_2O (3). Nevertheless, silent aspiration is a major problem during general anesthesia (13) and in the intensive care unit. Spray et al. (6) found silent aspiration in 20% of patients with high residual volume cuffs in ventilator treatment, whereas McCleave and Fisher (5) found only 1.5% silent aspiration among 200 patients. In a pediatric intensive care unit, aspiration occurred in one of nine older children intubated with cuffed tubes (4).

What are the dangers of silent aspiration? Lung damage after aspiration depends in part on the pH of the aspirate. If the pH is below 2.5, Mendelsohn's acid-aspiration syndrome can occur in adults with only 25–50 ml gastric juice (15). In laboratory experiments with excised tracheas, Pavlin et al. (1) found the leak around high residual volume cuffs to be 0.4–2.1 ml/min, with 20 cm H_2O cuff pressure. Severe lung damage is thus a possible complication to silent aspiration, even during short procedures and is probably the cause of some of the postoperative pulmonary complications in 20% of patients undergoing abdominal surgery (16).

Silent aspiration is an even greater problem in intensive care units. Colonization of the trachea is caused by silent aspiration in three out of ten patients with prolonged intubation (17). Because protection from bacterial contamination from ventilators and air did not reduce the rate of colonization of the trachea in intensive care unit patients, it was concluded that silent aspiration is probably the main cause of contamination (18).

In conclusion, the results from the present and other clinical investigations indicate that protection against silent aspiration is still a problem in clinical practice. However, silent aspiration may be prevented by using improved cuff design and control of cuff inflation. With high residual volume cuffs, the cuff pressure on the mucosa can be controlled and adjusted to minimize the risk of aspiration.

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Prolongation of Lidocaine Spinal Anesthesia with Phenylephrine

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The effect of added phenylephrine on the duration of sensory analgesia during lidocaine spinal anesthesia was determined in 65 ASA class I–III patients randomly divided into three groups. Group 1 (n = 25) received 62.5 mg lidocaine in 7.5% glucose; group 2 (n = 21) received lidocaine with 2 mg phenylephrine; and group 3 (n = 19) received lidocaine with 5 mg phenylephrine. The level of analgesia to pin prick was assessed by an anesthesiologist unaware of the drug combination used. The mean ± SD cephalad level of analgesia did not differ among the groups. In group 1, the times for two- and for four-segment regression of the level of analgesia, and the time for regression of analgesia to the T-12 dermatome, were 77 ± 19 (1 SD), 99 ± 24, and 109 ± 26 min, respectively. The corresponding values were 98 ± 25, 118 ± 27, and 130 ± 36 min in group 2 and 124 ± 32, 142 ± 31, and 162 ± 35 min in group 3. All the regression times in group 2 were significantly longer than those in group 1 (P < 0.05). All the regression times in group 3 were significantly longer than those in group 2 (P < 0.02). It is concluded that clinically useful prolongation of sensory analgesia may be obtained by addition of phenylephrine to lidocaine during spinal anesthesia.

Key Words: SPINAL ANESTHESIA—lidocaine. VASOPRESSORS—phenylephrine. SENSORY ANALGESIA.

It is generally believed that the addition of vasoconstrictor agents to local anesthetics prolongs the duration of spinal anesthesia (1–4). However, recent well-controlled studies suggest that clinically useful prolongation may depend on the specific local anesthetic–vasoconstrictor combination used (5–7). For instance, Chambers et al. reported that the addition of epinephrine to lidocaine or bupivacaine did not provide clinically meaningful prolongation of spinal anesthesia, and that phenylephrine failed to increase the duration of bupivacaine spinal anesthesia (5,6). On the other hand, they found that phenylephrine, but not epinephrine, increased the duration of sensory analgesia during tetracaine spinal anesthesia (7). Thus the results obtained for one drug combination probably cannot be applied to predict the duration of another. To our knowledge, the duration of clinically useful sensory analgesia produced by a phenylephrine–lidocaine combination has not been evaluated in humans. Therefore, the present study was designed to assess the possible role of phenylephrine on the duration of lidocaine-induced spinal anesthesia.

Methods

Sixty-five ASA class I–III men, undergoing cytoscopy or transurethral prostatic or bladder surgery with spinal anesthesia, were studied. After Institutional Human Experimentation committee approval, informed consent was obtained from each patient. Patients with neurologic impairment or those unable to communicate in English were not included. No patient received premedication. Lactated Ringer's solution (500–1000 ml) was infused intravenously in all patients prior to induction of spinal anesthesia. Baseline levels of blood pressure, pulse rate, and lead II ECG were recorded, after which all patients were placed in the left lateral decubitus position with maximum thoracolumbar flexion. Under sterile conditions, lumbar puncture was performed using a midline approach at the L3–4 intervertebral space, with a 25-gauge spinal needle. After obtaining a clear, free flow of cerebrospinal fluid (CSF), a mixture of local anesthetic in glucose with or without phenylephrine was injected over a period of 10 sec and the needle removed.

Based on the injected mixture of the drug, the patients were randomly divided into three groups. Group 1 (n = 25) received 62.5 mg, 5% lidocaine in 7.5% glucose; group 2 (n = 21) received 62.5 mg, 5% lidocaine in 7.5% glucose with 2 mg of 1% phenylephrine; and group 3 received 62.5 mg, 5% lidocaine in 7.5% glucose with 5 mg of 1% phenylephrine. The total injected volume of the local anesthetic solutions

were 1.25 ml, 1.45 ml, and 1.75 ml in groups 1, 2 and 3. Phenylephrine was carefully drawn up in a 1-ml tuberculin syringe, added to the hyperbaric lidocaine solution, and mixed thoroughly before injection. The pH of separately prepared local anesthetic–vaso-constrictor mixtures identical to those injected into each patient were measured using a previously cali-brated Fischer Scientific model 320 pH meter.

The patients were placed in supine horizontal po-sition immediately after injection of local anesthetic solution and removal of the spinal needle. Blood pres-sure, pulse rate, and ECG were monitored every 2 min for 10 min and thereafter every 10 min until the time of discharge from the recovery room. The level of sensory analgesia was assessed by the patient's verbal response to pain induced by pin prick using an 18-gauge needle on both sides of the trunk at the midclavicular line and the anterior aspect of the thigh. This was done every 2 min for 10 min after injection and every 10 min thereafter until analgesia to pin prick regressed to the T-12 dermatome. The level of sensory analgesia 10 min after subarachnoid injection was re-corded as the initial analgesic level. The times re-quired for analgesia to regress two and four segments from the initial level and the time for analgesia to regress to the T-12 dermatomal level was determined and recorded for each patient. A dermatomal chart was used for each patient to ensure accurate assess-ment of analgesic level. All assessments were done by an anesthesiologist who was unaware of the drug combination used. The operating table was main-tained horizontally during surgery, with the patients in lithotomy position. Postoperatively in the recovery room all patients were kept in supine, horizontal po-sition until they were discharged from the unit. In-traoperative and postoperative hypotension was treated by infusion of lactated Ringer's solution (200–500 ml) and/or ephedrine sulfate, 5–10 mg, intravenously.

Data were analyzed using one-way analysis of var-iance and Bonferroni t-test (8). Only two comparisons were made between the three experimental groups. Statistical significance was defined as $P < 0.05$.

Results

No significant difference existed among the groups with regard to age, weight, or height (Table 1). Mean $\pm$ SD cephalad spread of sensory analgesia was 9.5 $\pm$ 1.9 segments in groups 1 and 2, and 9.7 $\pm$ 1.16 segments in group 3, resulting in a T6–7 level. These differences were not significant. Maximum cephalad level of sensory analgesia was reached in all patients within 10 min after subarachnoid injection of local

Table 1. Patient Characteristics

	Lidocaine ($n = 25$)	Lidocaine + 2 mg phenylephrine ($n = 21$)	Lidocaine + 5 mg phenylephrine ($n = 19$)
Age (yr)			
Mean	68	69	69
Range	48–84	51–92	59–80
Weight (kg)			
Mean	65	65	66
Range	54–89	43–144	50–80
Height (cm)			
Mean	171	171	172
Range	163–185	155–184	159–183

anesthetic solution. The level of analgesia after 10 min did not increase further. Blood pressure and heart rate changes during the first 10 min after the injection were not different among the three groups.

The mean times required for two- and four-seg-ment regression of analgesia and regression to T-12 dermatomal level are shown in Table 2 and Figure 1. Addition of 2 mg phenylephrine to lidocaine pro-longed two-segment regression time by 27% ($P < 0.005$), four-segment regression time by 19% ($P < 0.02$), and regression of analgesia to the T-12 der-matome by 19% ($P < 0.05$). Increasing the dose of phenylephrine to 5 mg prolonged two-segment regression time by an additional 26% ($P < 0.01$), four-segment regression time by an additional 20% ($P < 0.02$), and T-12 regression of analgesia by an addi-tional 24% ($P < 0.01$).

The mean $\pm$ SD pH of plain lidocaine solution was 6.137 $\pm$ 0.024 at room temperature. Addition of 2 mg phenylephrine reduced the pH to 6.001 $\pm$ 0.019, and 5 mg decreased it to 5.872 $\pm$ 0.028.

Discussion

Our results show that addition of phenylephrine to lidocaine provides clinically useful prolongation of spinal anesthesia. These findings differ from those of Denson et al. (9), who demonstrated in primates pro-longation of motor blockade but no increase in du-ration of clinically useful sensory analgesia. The dis-crepancy is probably due to differences in methodology. Denson et al. evaluated 30 mg lidocaine with 1.5 mg phenylephrine in monkeys placed in a sitting position after local anesthetic injection. Our study used 62.5 mg lidocaine with 2 or 5 mg phenylephrine in patients who were kept supine or in the lithotomy position. In a pilot study conducted in humans we also noted that 1 mg phenylephrine failed to prolong lidocaine spinal analgesia. Finally, in spite of similarities found between humans and primates in sensory and motor

Table 2. Mean ± SD and Range of Regression Times of Analgesia for Each Test Group

Group	Dose of phenylephrine	Regression two segments[a] (min)	Regression four segments[a] (min)	Regression T12[a] (min)
1	none	77 ± 19 (35–100) $P < 0.005$[b]	99 ± 24 (45–155) $P < 0.02$[b]	109 ± 26 (50–140) $P < 0.05$[b]
2	2 mg	98 ± 25 (60–145) $P < 0.01$[c]	118 ± 27 (78–160) $P < 0.02$[c]	130 ± 36 (85–179) $P < 0.01$[c]
3	5 mg	124 ± 32 (77–180)	142 ± 31 (86–175)	162 ± 35 (95–245)

[a]Values are expressed as mean ± SD (range in parentheses).
[b]Bonferroni t-test, group 1 vs group 2.
[c]Bonferroni t-test, group 2 vs group 3.

responses to spinal anesthesia (10), accurate evaluation of sensory responses in monkeys may not always be possible.

Review of data from earlier reports fails to show a consistent dose–response relationship between the amount of added phenylephrine and duration of spinal anesthesia (2,11–16). Sergent et al. (12) noted 45% prolongation with 1 mg phenylephrine, whereas Bray et al. (11) and Moore et al. (1,2) showed 8 and 100% prolongation, respectively, with a 5-mg dose. This inconsistency has been attributed to the differences of experimental designs employed in these studies (17). By using rigorously controlled conditions, we were able to show a reasonably linear dose–response relationship. However, we noted a wide variability of duration among patients who received the same drug dose or combination. Although this finding may be a real individual variation of response, it may be also due to the subjective nature of the method used to determine sensory analgesia. The assessment of spinal cord function with somatosensory evoked cortical potentials may be a more objective method for this purpose.

The mechanism by which vasopressors prolong spinal anesthesia is not clear. Several mechanisms have been proposed. It is generally believed that vasoconstrictors prolong the duration of spinal anesthesia by limiting the vascular uptake of local anesthetics from CSF (17–19). Also, spinally administered epinephrine has been shown to produce sensory analgesia by direct action on the α-adrenergic inhibitory system of substantia gelatinosa (20). This mechanism, however, can explain an increase in intensity of analgesia but probably not a prolongation of analgesia. Currently, it is not known whether phenylephrine has such direct action. Finally, local anesthetic–vasoconstrictor mixtures are more acidic than the local

anesthetics alone (21). Thus it is likely that injection of these mixtures may reduce the CSF pH at the injection site. This may result in an increase in cationic fraction of the local anesthetic causing prolongation of blockade, particularly in the nonmyelinated nerve fibers (22). Nevertheless, Stark et al. (23) found that a bupivacaine–epinephrine mixture with much lower pH (3.781) than the mixture used in our study had very little effect on the CSF pH. Thus reduction of CSF pH may not have played a role on our results.

Why would phenylephrine and not epinephrine prolong lidocaine-induced spinal anesthesia? Concepcion et al. (24) showed that at equipotent doses epinephrine and phenylephrine were equally effective in prolonging the duration of tetracaine spinal anesthesia. The differences in results obtained using lidocaine–epinephrine (5) and lidocaine–phenylephrine combinations do not appear to be related to the use of doses of vasoconstrictors that are not equipotent. The 2-mg dose of phenylephrine used in our study was equipotent to the 0.2-mg epinephrine dose (24) used by Chambers et al. (5) and yet produced significant prolongation. One possible explanation may lie in the shorter action of epinephrine compared to that of phenylephrine (25). Converse et al. (26) showed that addition of epinephrine to tetracaine increased CSF tetracaine levels above those observed when epinephrine was not used. This was, however, most obvious only during the first 5 min after the injection and lasted no longer than 30 min. Also, intrathecal injection of epinephrine in dogs has been shown to decrease spinal cord blood flow only during the first 15 min, after which the blood flow returns to normal (27). Initial vascular absorption of intrathecally injected lidocaine seems to continue for 20–30 min and in 40% of the patients absorption may not even begin until 10 min after the injection (28). Thus epinephrine,
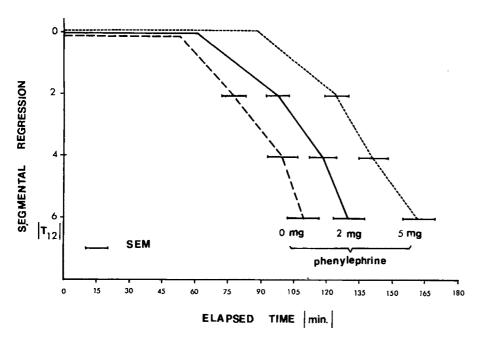
Figure 1. Mean ± se times of two segments, four segments, and T12 regression of sensory analgesia after subarachnoid injection of lidocaine with and without phenylephrine. For level of significance see Table 2.

with a short duration of action, may not effectively prevent this rather delayed but prolonged absorption of lidocaine. Phenylephrine, however, by producing sustained and longer lasting (>40 min) reduction of spinal cord and dural blood flow, may provide more effective prolongation of anesthesia (18,19).

Phenylephrine increases the duration of spinal anesthesia produced by lidocaine and tetracaine (7), but it does not prolong bupivacaine spinal anesthesia (6). This may be related to the differences in the extent of changes in spinal cord and dural blood flow with various local anesthetic agents. Crosby (29), in the awake rat model, demonstrated 27–34% spinal blood flow reduction with bupivacaine. Dohi et al. (18), in the dog model, could not demonstrate any spinal circulatory effect with subarachnoid lidocaine. Finally, Kozody et al. (30) found 150% increase of spinal cord blood flow with intrathecally injected tetracaine, which could be prevented by the addition of epinephrine. Although we do not know with what degree of certainty animal data can be applied to humans, these differences suggest that the efficacy of vasocontrictor agents in prolonging spinal anesthesia may be dependent on the spinal cord circulatory effects of concomitantly used local anesthetics.

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Review Article

Plasma Drug Binding:

Implications for Anesthesiologists

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The measurement of plasma drug concentrations is now a therapeutic tool widely applied in drug dosage adjustment. It is customary to measure total drug concentrations in either blood or plasma. However, total drug concentration exists in two forms: that which is bound to plasma proteins and other plasma constituents, and that which is free or unbound. The factors influencing drug binding and the pharmacokinetic and pharmacodynamic consequences of altered drug binding will be addressed in subsequent sections of this review.

After entry into the systemic circulation, drugs are transported by the blood to their sites of action, metabolism, and excretion. In blood, many drugs are bound to plasma proteins in a reversible manner which may be considered to obey the law of mass action,

$$[\text{Unbound drug}] + [\text{Protein}]$$
$$\underset{K_2}{\overset{K_1}{\rightleftharpoons}} [\text{Drug-protein complex}] \quad (1)$$

where K_1 and K_2 are the rate constants of the forward and reverse reactions respectively. However, in addition to plasma proteins, many drugs are also bound to other blood constituents, such as red blood cells, so that the determination of in vivo plasma drug binding in the laboratory is in reality a measure of total plasma binding, and cannot be confined to particular protein fractions alone.

The degree of protein binding has important pharmacokinetic and pharmacodynamic implications, because it is the unbound moiety that readily diffuses across biological membranes, reaches the receptor site

to produce pharmacologic effect, and is most readily available for elimination from the body. To maintain the equilibrium between free and bound drug, a decrease in free drug concentration results in dissociation of the drug–protein complex, so that more free drug is then available to cross the cell membrane. Thus the interaction of most drugs with plasma proteins is a dynamic, reversible process, and dissociation of bound drug from the drug–protein complex occurs very rapidly.

The degree of plasma binding is often expressed as *percentage of drug bound*; thiopental, for example, is approximately 84% bound to the various plasma constituents (16). Another term frequently used is the *free fraction* of drug in plasma or serum; this is equal to the free drug concentration divided by the total drug concentration, i.e., divided by the bound drug concentration plus the free drug concentration. The free fraction of thiopental in plasma is therefore 16%.

Methodology

The extent of plasma drug binding is usually determined by one of two methods, equilibrium dialysis or ultrafiltration (20); of these methods, equilibrium dialysis is the more widely used. In this technique, plasma or protein solution is allowed to equilibrate with a protein-free solution (usually phosphate buffer). The plasma and buffer are separated by a semipermeable dialysis membrane of a pore size that does not allow protein to pass through but which allows unbound drug to pass freely. A known concentration of drug is added to the buffer, and once equilibrium has been achieved the free fraction of drug in plasma is equal to the concentration of drug in the protein free solution (buffer, dialysate) divided by the concentration in the plasma. Because the free concentration of drug under study is often relatively low, radiolabeled

drug is often used. This procedure is simple and precise and can be carried out on relatively small samples.

If a solution of drug and protein is exposed under pressure to a semipermeable membrane, a protein-free phase or filtrate containing only free drug will collect beyond the membrane—a process known as ultrafiltration. Knowledge of the initial concentration of drug present and the concentration of drug in the ultrafiltrate allows calculation of the degree of drug binding. The major advantage of this technique is its speed, but a potential disadvantage of ultrafiltration is that the protein concentration changes due to loss of fluid volume into the ultrafiltrate. A modification of ultrafiltration, diafiltration, involves a system in which lost volume is replaced, thereby avoiding concentration changes. It is generally accepted that equilibrium dialysis and ultrafiltration techniques are equivalent, and yield similar results (5,6,12,138).

In the past, binding studies have often been carried out in vitro, using buffer systems at nonphysiologic pH and temperature, which may affect drug binding. The pH of the serum or plasma can markedly effect lidocaine plasma binding, for example, such that as the pH is increased, the binding of lidocaine increases (100). Similarly, meperidine binding is also increased in a pH-dependent fashion (76). In addition, meperidine binding is influenced by temperature so that an increase in temperature results in a decrease in meperidine binding (76). Therefore, plasma binding determinations are critically dependent on both adequate pH and temperature control. Another problem has been the frequent use of inappropriate drug concentrations. Because the free fraction may be relatively low and, therefore, at usual therapeutic concentrations the free concentration will be below the sensitivity of the assay, investigators have sometimes used drug concentrations far in excess of those seen when the drug is used in clinical practice, which may give misleading results due to nonlinear binding. When the amount of drug in plasma is increased, the capacity of the available binding sites is exceeded and there may be a large increase in concentration of free drug, with the result that at high, possibly toxic, concentrations the free fraction may be unexpectedly high. This may have a profound effect upon the pharmacokinetics and toxicity of the drug. For these reasons, drug binding should ideally be determined at physiologic pH and temperature, and using drug concentrations within a range associated with therapeutic use.

Many drug binding studies have used albumin and other protein fractions from various animal species and extrapolated from these results to man. However, studies of drug binding even in purified human albumin solutions may not always predict binding to human plasma under physiologic conditions; for example, measurement of the binding of pancuronium in purified albumin and globulin solutions predicted that pancuronium would be highly bound with a free fraction of 13% (128). In fact, however, pancuronium binding in human plasma is low, with a free fraction of 93.2% (145).

Although the binding of drug in human plasma can be measured in vitro, there is no method for direct in vivo measurement of drug binding. However, by utilizing the fact that cerebrospinal fluid and saliva are relatively protein free, it is possible to use cerebrospinal fluid (CSF)/plasma or saliva/plasma drug concentration ratios as reflecting the free fraction of drug in vivo. The relevance of the in vitro determination of protein binding by a technique such as equilibrium dialysis can then be determined by correlating the in vitro measurement with the in vivo measurements.

Little attention has been given to the binding of drugs by erythrocytes, or indeed to the area of whole blood drug binding in general. It is blood, not plasma, that brings the drug to the particular organ for clearance, and as the drug equilibrates very rapidly between the red blood cell and plasma, whole blood binding has more clinical and physiologic relevance than plasma binding (77,117). Plasma drug binding is technically much easier to carry out than drug binding to whole blood; therefore, many investigators have utilized blood-to-plasma concentration drug ratios to estimate whole blood binding, rather than directly determining drug binding to whole blood.

A number of methodological problems need to be taken into account when measuring plasma drug binding. The technique by which blood is collected prior to the determination of plasma protein binding is important. The binding of certain basic drugs is inhibited in blood collected in vacutainer tubes (23,67), because a plasticiser in the cap, trisbutoxyethyl phosphate ester (TBEP), increases the free fraction by displacing drug from a binding protein, α_1 acid glycoprotein (11). The majority of vacutainer tubes are now produced without TBEP in the stoppers. Heparin is often used by clinical investigators both as an in vitro anticoagulant and to flush indwelling catheters to prevent clotting—the "heparin lock". Heparin increases plasma free fatty acid concentrations through activation of lipoprotein lipase (48), and a number of studies have shown that drug binding is lower after heparin administration (70,125,143). It appears that because heparin has only minimal effects on drug binding in vitro (139), the lipoprotein lipase-induced increase in nonesterified fatty acids is responsible for

Table 1. Drugs Binding to α_1-Acid Glycoprotein

Drug	Reference
Quinidine	Fremsted et al. Eur J Clin Pharmacol 1976;10:441-4.
Propranolol	Piafsky et al. N Engl J Med 1978;299:1435-9.
Methadone	Romach et al. Clin Pharmacol Ther 1981;29:211-7.
Lidocaine	Piafsky and Knoppert. Clin Res 1978;26:836A.
Etidocaine	Piafsky and Knoppert. Clin Res 1978;26:836A.
Bupivacaine	Denson et al. Clin Pharmacol Ther 1984;35:409-15.
Imipramine	Piafsky and Borga. Clin Pharmacol Ther 1977;22:545-9.
Chlorpromazine	Piafsky et al. N Engl J Med 1978;299:1435-9.
Meperidine	Nation. Clin Pharmacol Ther 1981;29:472-9.
Prazosin	Rubin and Blaschke. Br J Clin Pharmacol 1980;9:177-182.
Alprenolol	Piafsky and Borga. Clin Pharmacol Ther 1977;22:545-9
Disopyramide	Piafsky. Clin Pharmacokinet 1980;5:246-62.
Dipryidamole	Kopitor and Weisenbieger. Arzneimittelforsch 1971;6:859-62.
Verapamil	McGowan et al. Clin Pharmacol Ther 1983;33:485-90.
Alfentanil	Meuldermans et al. Arch Int Pharmacodyn 1982;257:4-19.

Table 2. Pathophysiologic States Associated with Alterations in Plasma Proteins to which Drugs Are Bound

Decreased albumin	Increased AAG	Decreased AAG
Burns	Burns	Neonates
Renal disease	Crohn's disease	Oral contraceptives
Hepatic disease	Renal transplantation	Pregnancy
Inflammatory Disease	Infection	
Nephrotic Syndrome	Trauma	
Cardiac failure	Chronic pain	
Postoperative period	Myocardial infarction	
Malnutrition	Postoperative period	
Malignancy	Malignancy	
Neonates	Rheumatoid arthritis	
Elderly	Ulcerative colitis	
Pregnancy		

the observed decrease in binding. Further studies have shown that activated lipoprotein lipase in plasma continues to liberate free fatty acids after blood sampling and even during equilibrium dialysis at 37° C. In contrast, the free fatty acids are cleared rapidly in vivo, so that after heparin administration, the free fraction of drug measured in vitro does not reflect the in vivo situation (15). It is essential that heparin not be administered prior to obtaining blood samples for drug binding studies; otherwise falsely high free fractions will be determined.

Binding Proteins

The three major proteins responsible for drug binding in plasma are albumin, α_1 acid glycoprotein (AAG), and the lipoproteins. Drugs may bind to more than one plasma protein. Prednisolone, for example, binds to albumin, AAG, and transcortin, whereas fentanyl and its analogues have been shown to bind to albumin, AAG, and to some extent α- and β-globulin fractions (87).

Albumin, the major binding protein, which constitutes about 60% of the total plasma protein concentration, binds a wide variety of drugs, such as sulfonamides, penicillins, and benzodiazepines, and also many endogenous compounds such as fatty acids and bilirubin. Most acidic drugs are bound in plasma to albumin. Although basic drugs do bind to albumin

to some extent, the binding in plasma of many such drugs, for example propranolol, lidocaine, quinidine, and chlorpromazine, is too great to be accounted for by their binding to albumin alone. Recent work has shown that the principal binding protein for a large number of basic or cationic drugs is AAG, also known as orosomucoid. Table 1 lists a number of drugs known to bind avidly to AAG. AAG is an acute phase reactant protein, the plasma levels of which become elevated in disease states such as inflammation or malignancy (Table 2). Thus it has recently been recognized that changes in plasma AAG concentrations in certain disease states may be responsible for changes in the degree of protein binding of a large number of basic drugs that are bound to this protein in plasma (98,121). Chronic inflammatory diseases, such as rheumatoid arthritis and Crohn's disease, are associated with an increase in AAG and hence an increase in the bound fraction of drugs such as chlorpromazine and propranolol, both of which are highly bound to this protein (99) (Fig. 1). Surgery (45), trauma (39), and chronic pain (46) are also associated with elevated plasma AAG concentrations.

Drugs may also bind to other plasma proteins, such as globulins and lipoproteins. Tubocurarine and pancuronium, for example, bind to isolated globulin solutions (128,50). Plasma lipoproteins that transport fatty acids, triglycerides, phospholipids, and cholesterol may also be responsible for some of the binding of certain basic drugs, such as chlorpromazine and imipramine (7). As mentioned earlier, drugs may also bind to red blood cells (7). Propranolol, for example, is thought not only to bind to plasma proteins, such as AAG, but also to enter the red blood cell according to the basic pharmacologic principles that affect drug
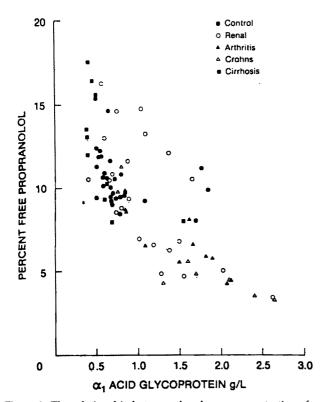
Figure 1. The relationship between the plasma concentration of α_1-acid glycoprotein and the percentage of free propranolol in 78 patients and healthy volunteers ($r = -0.77$; $P < 0.001$). (Reproduced from reference 99 with permission.)

passage across membranes, namely the extent of protein binding, ionization, and lipid solubility, so that the ratio of drug concentration in whole blood to that in plasma (the B/P or blood to plasma ratio) is linearly related to the fraction of propranolol free in plasma (144) (Fig. 2).

Binding Sites and Affinity

Drugs and endogenous small molecules bind to proteins in the blood and tissues according to the law of mass action (Equation 1). Quantitatively, binding may be analyzed in terms of the number of binding sites (n) and the equilibrium association constant (K_a), which is a measure of affinity.

From Equation 1,

$$\frac{[\text{Drug–Protein Complex}]}{[\text{Unbound Drug}] \times [\text{Protein}]} = \frac{K_1}{K_2} = K_a \quad (2)$$

The ratio of the rate constants K_1/K_2 is termed the equilibrium association constant (K_a), and the larger this value, the greater the affinity of the drug for the protein. Affinity may also be expressed in terms of the dissociation constant (K_d), which is the reciprocal

of affinity and is equal to K_2/K_1. There may be only one binding site on each protein molecule, or there may be several binding sites (n) on the protein molecule. These binding sites may be of more than one class, each with its own affinity. The unbound drug concentration is dependent on the number of binding sites (n), the total protein concentration, and the dissociation constant (K_d) (Fig. 3).

In vitro studies of the binding of drugs to proteins in plasma or to isolated proteins provide information on the nature and numbers of binding sites. Drug binding is measured over a range of drug and/or protein concentrations. A Scatchard analysis is often used (Fig. 4). When the compound binds to a single class of binding sites a straight line will be obtained with a slope of $-K_a$. The number of binding sites can be determined from the x intercept. Curvilinear plots are produced if there are two or more classes of binding sites each with different affinity.

In the case of many drug–albumin interactions, there are often one or two primary binding sites (high affinity) together with a variable number of secondary (lower affinity) sites. Attempts have been made to locate and classify the binding sites on human serum albumin. Specific binding sites have been identified for the endogenous compounds bilirubin and tryptophan. Albumin appears to have at least three drug binding sites, which can be identified using radiolabeled marker drugs. Diazepam, digitoxin, and warfarin bind to separate sites on the albumin molecule, and thus these three drugs have been used as markers to characterize these three discrete binding sites, and to correlate the binding of other drugs to these sites on the albumin molecule (123). The antiepileptic, sodium valproate, is highly bound in plasma (87–94%) to both the diazepam and warfarin binding sites on albumin (72). Phenytoin, on the other hand, binds to the warfarin site (Fig. 5) (72). Valproate and phenytoin are frequently coadministered, and this results in the displacement of phenytoin from the warfarin site, producing an increase in the free fraction of phenytoin. Since the plasma concentrations of valproate achieved by the high therapeutic doses are so much higher than those of phenytoin, phenytoin has little effect on valproate binding. By the use of three markers (diazepam, digitoxin, and warfarin) it is possible to determine which binding sites a drug uses, the nature of the binding sites on albumin, and the affinity or K_a of the drug–albumin complex, and to predict the likelihood of drug–drug displacement, with drugs bound to the same binding site being most likely to displace one another. Benzodiazepines, penicillin derivatives, and some antidiabetic agents displace diazepam, whereas other drugs such as diuretics, phe-
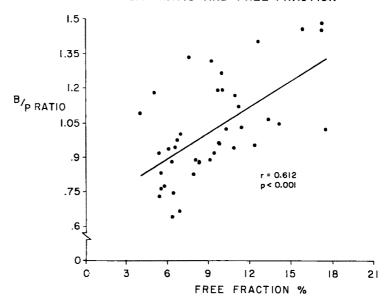
B/P RATIO AND FREE FRACTION

Figure 2. The relationship between the blood/plasma (B/P) ratio and free fraction of propranolol in plasma during cardiopulmonary bypass. As the free fraction increases, more propranolol enters the red cells, causing the B/P ratio to increase. (Reproduced from reference 144 with permission.)

nytoin, salicylic acid, and bilirubin displace warfarin. Displacement of digitoxin by other drugs is uncommon.
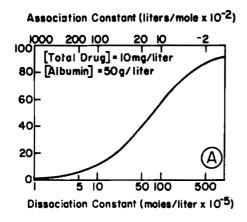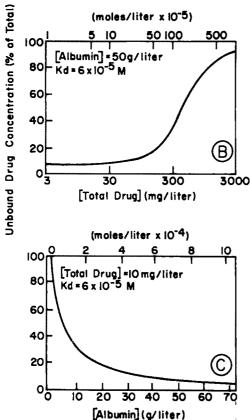
Factors Affecting Drug Binding

Age and Pregnancy

The plasma binding of drugs in the pregnant patient and fetus or newborn infant is important, because placental drug transfer is predicated by the free fraction of drug in plasma. Newborn infants and pregnant women have reduced levels of plasma albumin (47), and in the neonate plasma AAG concentrations are markedly reduced compared to concentrations seen in adults (146) (Fig. 6). The binding of many acidic drugs is reduced in late pregnancy (19,30,97). Low plasma albumin concentrations may contribute to reduced binding of some drugs in neonates, but there is also evidence that neonatal albumin may have a reduced affinity for many drugs (135). The free fraction of propranolol (146), lidocaine (130,146), bupivacaine (127), meperidine (90), ampicillin (40), phenobarbital (40), phenytoin (40), imipramine (101), diazoxide (101), d-tubocurarine (146), and metocurine (146) are all greater in umbilical cord plasma than in adult plasma. Pancuronium binding is unchanged in the neonate (145). For meperidine, bupivacaine, lidocaine, and propranolol (which are known to avidly bind to AAG) the increased free fraction in the neonate is due to the decreased plasma AAG concentration. In contrast, the free fraction of diazepam, which principally binds to albumin, has been shown to be higher in maternal plasma than in umbilical venous

plasma (91,111,146). In addition, compared to nonpregnant women, pregnant women have decreased diazepam binding. Differences in diazepam binding in pregnancy and the newborn can be explained by higher free fatty acid concentrations and lower albumin levels in the maternal plasma (110). Thus it is possible from a knowledge of a drug's principal binding protein (albumin or AAG) to predict alterations in plasma drug binding in mother and newborn.

At the other age extreme, plasma albumin concentrations tend to be lower (27,133,137), whereas plasma AAG concentrations tend to increase with age in some studies (27,133). The binding of a number of drugs is altered in the elderly, with the free fraction of thiopental (69), etomidate (17), and temazepam (35) being increased. The binding of midazolam (57), lidocaine (27), propranolol (133), and meperidine (64,66,133) is, however, unchanged in the elderly. The effects of age on diazepam binding are conflicting (27,58,71), but when changes in diazepam binding have been shown, they appear to reflect alterations in serum albumin with increasing age. It is important to recognize that binding changes in healthy elderly patients are small compared to the larger changes in plasma protein binding produced by disease states.

Sex

Plasma albumin concentrations decrease with increasing age in both men and women; however, there appears to be no significant sex-related difference (133). In addition, plasma AAG concentrations in men and

Figure 3. The effect of changes in dissociation constant (A), total drug concentration (B) and albumin concentration (C) on drug binding. (A) At any given drug and albumin concentration the unbound fraction increases with decreasing affinity (increasing K_d). (B) For any given affinity, the fraction of free drug increases as total drug concentration increases. (C) For any given affinity, the fraction of free drug increases as albumin concentration decreases. (Reproduced from reference 73 with permission.)

Figure 4. Scatchard plot of r/D plotted against r, where r is moles of drug bound per mole of total protein and D is the free drug concentration. This is a straight line plot for a single class of binding sites and allows the calculation of Ka and n.

nonpregnant women are not significantly different, whether the latter are taking oral contraceptives or not (146). The plasma binding of d-tubocurarine (146), metocurine (146), propranolol (146), lidocaine (114,146), oxazepam (59), diazepam (114,146), chlorpromazine (133), desipramine (133), and phenytoin (133) do not differ between sexes; but diazepam and lidocaine free fractions are greater in nonpregnant women taking oral contraceptives than in age-matched women not using oral contraceptives (114,146). In summary, sex difference plays little role in contributing to alterations in plasma drug binding.

Disease States

Alterations in drug protein binding have been observed in a number of pathologic states (104,129). Disease-related alterations in binding may be due to changes in the binding protein concentration (AAG and albumin), altered binding affinity, modification of the degree of ionization of drug and protein, and competitive interactions between drug and endogenous ligands, such as the inhibition of binding due to increased free fatty acid concentrations.

Renal disease. Acidic drugs tend to selectively bind to albumin. Since hypoalbuminemia and reduced binding capacity of albumin occur in chronic renal disease, this may lead to reduced plasma binding of acidic drugs (36,103,106). In renal disease, however, even in the presence of normal plasma albumin concentrations, the binding of some drugs is reduced; an example of this is phenytoin (107). The degree of plasma binding of phenytoin correlates with the severity of renal failure, as assessed by blood urea nitrogen or serum creatinine concentrations (105,107). The correlation of the decreased binding of phenytoin with the severity of azotemia independently of hypoalbuminemia suggests that low albumin concentrations are not sufficient explanation for the decrease in phenytoin binding observed in plasma from uremic patients. It may be due to occupation of protein binding sites either by some metabolic product that is nor-
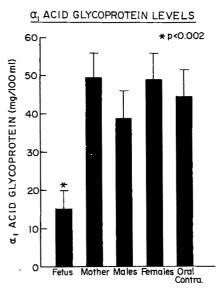
Figure 5. The binding of drugs to two sites on human serum albumin. (Reproduced from reference 72 with permission.)

Figure 6. Mean α_1-acid glycoprotein concentrations ($\pm$ SEM) in maternal, fetal, male and nonpregnant female subjects, and women taking oral contraceptives. (Reproduced from reference 146 with permission.)

mally excreted by the kidney (34), or by nonesterified free fatty acids that are present in increased amounts in uremic patients, especially after heparin administration during hemodialysis. Another explanation might be that an alteration in protein structure occurs in renal disease. Organic acids such as phenytoin (92), sulfonamide (3), thyroxine (103), clofibrate (103), salicylate (103), thiopental (16,103), diazoxide (94), phenylbutazone (103), etomidate (18), and benzylpenicillin (103) all exhibit decreased binding in plasma from patients with poor renal function.

The plasma binding of basic drugs in patients with renal disease may be normal, decreased, or increased. Alterations in the binding of basic drugs in patients with renal disease depend on both the relative contribution that albumin and AAG make to the drug's total binding and on the type of the patient's renal disease. Thus in uremic patients, nephrotic patients, and recipients of renal transplants, the binding of diazepam, which is bound principally to albumin, is reduced, presumably on the basis of reduced plasma albumin concentrations (60,61). In contrast, the binding of lidocaine, which is bound principally to AAG, increases in uremic patients and transplant recipients, but does not change in nephrotic patients (60), possibly due to the fact that the plasma AAG concentrations are elevated in uremic and transplant recipients but not in nephrotic patients, who generally have decreased albumin concentrations and normal plasma AAG concentrations. Propranolol and chlorpromazine binding is increased in patients with inflammatory renal disease who have elevated AAG concentrations (99). Morphine binding is slightly decreased in patients with poor renal function (93).

The protein binding of the muscle relaxants pancuronium (145) and d-tubocurarine (49,134) is not affected by renal disease. Table 3 shows the changes in plasma protein pattern in various types of renal disease, and presents a general hypothesis for the changes in plasma drug binding that occur.

Hepatic disease. In patients with liver disease, while plasma albumin concentrations are frequently reduced, globulin fractions may be increased. In addition, the accumulation of endogenous substances, such as bilirubin, may result in competition for drug binding sites (8). Knowledge of the fundamental mechanisms of altered plasma binding for a particular drug in patients with hepatic disease is incomplete, and altered plasma binding probably is the result of a complex, multifactorial pathologic process that differs in extent from individual to individual, thereby making prediction difficult. Results of studies of binding of various drugs in patients with liver disease have varied from study to study, probably because of differences in types of liver disease and plasma protein concentrations in the subjects studied. The binding of a large number of drugs, including morphine (93), diazepam (126), tolbutamide (126), phenylbutazone (136), etomidate (18), phenytoin (93), thiopental (52), quinidine (1), and amylobarbital (85), are decreased in patients with liver disease. Meperidine (81) and lidocaine (142) binding appears to be unchanged. The protein binding of the neuromuscular blocking agents tubocurarine, fazadinium, pancuronium, and vecuronium is unaffected by cirrhosis (38,49,134).

Burn injury. There are marked changes in plasma drug binding after severe burn injury. Albumin concentrations may be the same or fall after thermal injury (119), whereas the plasma concentration of AAG increases (83). The binding of imipramine increases and the free fraction decreases after severe burn in-

Table 3. Effect of Renal Disease and Change in Plasma Protein Pattern on Plasma Drug Binding

	Chronic renal failure; uremia	Inflammatory renal disease	Nephrotic syndrome	Transplant recipients
Albumin	↓	↓ ↓	↓	↓ or near normal
AAG	↑	↑ ↑	—	↑
Free fraction of acidic drugs (albumin bound)	↑	↑	↑	↑ or near normal
Free fraction of basic drugs (AAG bound) e.g., lidocaine propranolol	↓	↓	—	↓
Free fraction of basic drugs (albumin bound) e.g., diazepam	↑	↑	↑	↑

jury, the latter correlating with increased AAG concentrations. In contrast, the free fraction of diazepam, which is largely albumin bound, is greater in burned patients than in normal subjects, presumably due to their decreased albumin levels (9,83). d-Tubocurarine binding is increased after thermal injury (78).

Myocardial infarction. Increases in plasma AAG concentrations have been noted in myocardial infarction patients admitted to the coronary care unit but not in patients admitted in whom myocardial infarction was later ruled out (115). Total plasma lidocaine concentrations increase with time in patients with myocardial infarction who receive constant infusions of the drug (113). Increased lidocaine binding occurs in these patients, probably due to the observed alterations in plasma AAG concentrations. It is unclear whether these binding changes are also responsible for the observed increase in lidocaine concentrations, but they may partly account for these changes. The increase in plasma AAG concentrations after myocardial infarction is also associated with an increase in plasma propranolol binding (116).

Surgery

Marked changes in physiology and metabolism occur after trauma and surgery. During the catabolic phase after trauma, there is increased nitrogen loss with increased albumin breakdown and distribution into the extravascular space (41). These changes result in a decrease in plasma albumin concentration after surgery, whereas globulin concentrations may increase, with a resultant decrease in the albumin:globulin ratio (41). Plasma levels of free fatty acids markedly increase in the first 24 hr postoperatively (41). Plasma AAG concentrations increase after surgery (45) and trauma (39) while plasma albumin concentrations decrease (41). All these changes might be expected to contribute to altered drug binding, and phenytoin binding, for example, has been shown to decrease after surgery (42), probably subsequent to a decrease in albumin concentration, although competitive in-

hibition by endogenous substances such as free fatty acids may also be important. In contrast, the binding of the basic drug quinidine, which binds to AAG, is increased in keeping with the elevation in AAG (45). Also, the increase in plasma AAG concentrations seen after trauma is associated with a decrease in lidocaine free fraction. Plasma AAG concentrations, which reach a peak 10–14 days after injury, are more than three times normal levels. Propranolol binding increases 24 hr after surgery, possibly due to postoperative elevation in plasma AAG concentrations (44). Lidocaine binding after cardiac surgery also increases, the lidocaine free fraction decreasing from 30.2% prior to surgery to 16.4% 3 days after surgery (65). This decrease in lidocaine free fraction coincides with a 200% increase in plasma AAG concentration (65). Albumin concentrations also decrease slightly after cardiac surgery, probably as a result of the combined effects of cardiopulmonary bypass, hemodilution and the postoperative catabolic state.

The effects of cardiac surgery and cardiopulmonary bypass on the measurement of drug protein binding are complex. Heparin administration during cardiopulmonary bypass causes the release of lipoprotein lipase and increases free fatty acid concentrations (54,144); free fatty acids have been shown to competitively inhibit drug binding. Although in vivo it appears that the clearance of free fatty acids may be rapid enough for protein binding to be little affected, in vitro, after sampling, the lipoprotein lipase continues to liberate free fatty acids. If heparin is administrated prior to sampling, plasma levels of free fatty acids are elevated six-fold (144). However, if lipoprotein lipase activity is inhibited in vitro, only a 15–20% increase occurs in free fatty acid concentrations (54). This increase in free fatty acids in vitro after sampling, by competing for drug binding sites, causes a large decrease in the measured binding of propranolol and quinidine (125,144). Because the free fatty acids increase principally after blood sampling, however, this change in findings probably does not alter drug disposition in vivo.

The hemodilution associated with cardiopulmonary bypass may also affect drug binding, not only because of hemodilution per se, but also because of the nonphysiologic protein concentrations in the pump prime. Plasma albumin concentrations fall markedly during cardiopulmonary bypass (24). Simulation in vitro of the effects of hemodilution due to the pump prime shows a small increase in propranolol free fraction, from 10.3 to 14.1% (144).
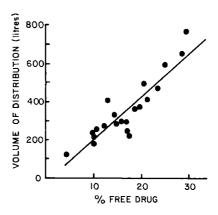
Anesthesia

Volatile anesthetics in high concentrations can cause structural changes in proteins, including albumin (4), which may alter the drug binding capacity of the protein. Enflurane, halothane, and the halothane metabolite, trifluroacetic acid, have been shown to displace diazepam in vitro from human serum albumin (26). Enflurane (1.0 MAC) also decreases the binding of diazepam in vitro, with a resultant increase in serum free fraction of 60% (26). The binding of propranolol and prazosin in serum is unaffected by the in vitro addition of either halothane of enflurane. A small but significant reduction in plasma propranolol binding occurs during halothane (2.0 MAC) anesthesia in the dog (108). Thus information on the effects of the inhalational anesthetics on drug binding in vivo is presently limited and requires further investigation.

Effect of Binding on Drug Disposition

Distribution

It is the free or unbound drug that equilibrates across cell membranes, so that at equilibrium the drug concentration throughout extracellular water will equal the unbound concentration in the plasma. In general, the greater the degree of protein binding, the less of the drug will be available to leave the plasma space, and hence the smaller the volume of distribution will be. Figure 7 shows the relationship between the volume of distribution of propranolol and the unbound fraction, indicating that the volume of distribution increases as the free fraction increases (13). The apparent volume of distribution (Vd) thus gives an indication of the extent of binding and distribution of a drug (55).

The plasma or serum concentration used in the calculation of Vd is usually total drug concentration. Because only free drug leaves the plasma and equilibrates with the rest of the body, the use of total drug concentration may mask changes in distribution of
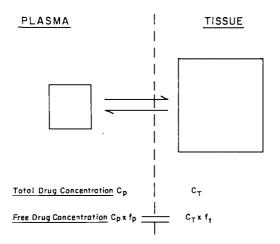
Figure 7. The relationship between the volume of distribution of propranolol and the unbound fraction (% free drug) in normal and diseased subjects. (Reproduced from reference 13 with permission.)

unbound drug in the case of drugs that are bound to plasma proteins. For drugs that are highly protein bound, it may be important to calculate the volume of distribution of free drug on the basis of plasma or serum concentration of free drug. The effect of protein binding on volume of distribution can be illustrated using thiopental as a prototype. The free fraction of thiopental in plasma is increased from 15.7% in normal subjects to 28% in patients with renal failure, indicating decreased thiopental binding in patients with renal disease (16). This results in more drug being available for tissue distribution and an increased volume of distribution (calculated using total drug concentration) in renal failure patients (3.0 L/kg) as compared to normal patients, where the volume of distribution is 1.9 L/kg. If tissue binding is unchanged, the volume of distribution of free drug will be independent of binding, and, in the case of thiopental, the unbound volume of distribution at steady state based on free drug concentrations is similar in both patients with normal (12.0 L/kg) and impaired (11.5 L/kg) renal function.

The measurement and interpretation of drug binding in tissues is an area that is currently one of great interest (140), as new techniques for tissue binding measurement are developed. Present data in the literature rely mainly on laboratory animal models or post mortem tissue analysis. Obviously, tissue binding measurement in humans is invasive, but research in this area may yield new insights into the effects of altered tissue binding on drug kinetics and displacement interactions.

Consider, at equilibrium, the free concentration of drug in plasma and tissue to be equal (Fig. 8).

$$C_p \times f_p = C_T \times f_t$$

PLASMA | TISSUE

Total Drug Concentration C_p | C_T

Free Drug Concentration $C_p \times f_p$ ═══ $C_T \times f_t$

Figure 8. The relationship between free drug concentration in plasma and in tissue. The free concentration in plasma equals the total concentration (C_p) × the free fraction in plasma (f_p). The free concentration in tissue equals the total concentration in tissue (C_T) × the free fraction in tissue (f_t).

and thus:

$$C_T = C_p \times \frac{f_p}{f_t}. \tag{3}$$

But tissue volume of distribution

$$= \frac{\text{Total amount of drug in tissue}}{C_p}$$

$$= \frac{V_T \times C_T}{C_p}.$$

Substituting from Equation 3 $= V_T \times \dfrac{f_p}{f_t}$.

Thus:

$$Vd_{ss} = V_p + V_T \left[\frac{f_p}{f_t}\right] \tag{4}$$

where C_p = total concentration in plasma, C_T = total concentration in tissue, Vd_{ss} = volume of distribution at steady state, V_p = plasma volume, V_T = tissue volume, f_p = fraction of drug free in plasma, and f_t = fraction of drug free in tissues.

Thus, from Equation 4, volume of distribution is dependent on both plasma and tissue binding. For very lipid soluble drugs, which are equally bound in plasma and tissue and therefore readily cross cell membranes, the volume of distribution of free drug will be equal to total body water. Thus, to take the simplest example of a drug whose binding is equal in plasma and tissue such that $f_p = f_t$; since $f_p/f_t = 1$, $Vd_{ss} = V_p + V_T$ = i.e., total body water (from Equation 4).

For drugs that are not very lipid soluble and do not readily cross cell membranes, the volume of dis-

tribution of free drug will be equal to the extracellular space. The smallest possible volume of distribution is equal to plasma volume. A volume of distribution equal to plasma volume would theoretically occur not only when there is such extensive plasma protein binding that the fraction of free drug in plasma (f_p) approaches zero, but also when there is almost no tissue binding so that the free fraction in tissues (f_t) approaches 100%. Thus, from Equation 4, if $f_p \rightarrow 0$, then $Vd_{ss} = V_p$. Drugs that are highly bound to plasma proteins but less bound to tissue ($f_p/f_t < 1$) have volumes of distribution that are greater than plasma volume but less than the volume of total body water. In contrast, drugs that are more extensively tissue bound than plasma bound ($f_p/f_t > 1$) have volumes of distribution that are greater than the volume of total body water. For drugs that are extensively tissue bound, the fraction of free drug in tissues (f_t) will be low, say 1%, and the fraction of free drug in plasma (f_p) will be high, say 100%. Thus, if $f_p/f_t > 1$, then $Vd_{ss} = V_p + V_T$ [100/1] (from Equation 4). However, $V_p + V_T$ is approximately equal to total body water; therefore, Vd_{ss} is 100 times larger than the volume of total body water, demonstrating that for drugs that are highly tissue bound, Vd is larger than total body water.

Antipyrine, which has minimal plasma or tissue binding so that both f_p and f_t approach 100%, has a volume of distribution almost equal to the volume of total body water ($f_p/f_t = 1$, $Vd_{ss} = V_p + V_T$).

The degree of plasma drug binding has an important effect on drug distribution in mother and fetus, because only the free, i.e., unbound, drug readily crosses the placenta. The plasma binding of bupivacaine is higher in maternal plasma than in neonatal plasma (due to lower AAG concentrations in the neonate), and at delivery, after the epidural administration of bupivacaine to the mother, the total umbilical venous plasma concentration of bupivacaine is lower than the total maternal venous plasma concentration (127). Bupivacaine is highly bound in the mother, and only a small free fraction is available for distribution across the placenta. However, the concentrations of free bupivacaine in umbilical venous and maternal venous plasma at delivery are the same. Once equilibrium is established, the free concentrations on each side of the placenta are the same. Because it is free drug that is available for binding to receptor sites and eliciting pharmacologic effects, these effects will be similar despite disparate total plasma or blood concentrations of drug in mother and neonate. This is an important source of confusion, as drugs are sometimes advocated as being safer for administration during labor based on lower total concentrations in the neonate, without taking into account the effects of

differences in plasma binding in the mother and fetus, which may negate differences in total drug levels.

Half-life

The elimination half-life ($t_{1/2}$) of a drug is dependent on both the volume of distribution (Vd) and the clearance (Cl) of that drug, because

$$t_{1/2} = \frac{0.693Vd}{Cl}. \quad (5)$$

Changes in binding can affect volume of distribution and clearance, sometimes in opposite directions, so that it is difficult to predict the overall effect of binding changes on a half-life.

The decrease of thiopental plasma protein binding in patients with chronic renal failure described above results in increases in clearance and volume of distribution at steady state when total drug concentrations are used for calculations (16). The terminal elimination half-life of thiopental was, however, unchanged in this study because of the similar changes in clearance and volume of distribution (Equation 5).

Hepatic Clearance

Drugs can be classified into two broad groups depending upon the rate at which they are removed as they pass through the liver. Drugs such as propranolol, morphine, and lidocaine, which are efficiently removed from the blood by the liver, are known as high extraction drugs, whereas drugs that are poorly removed by the liver, such as warfarin and tolbutamide, are considered low extraction drugs. Low extraction drugs are classically conceptualized as having kinetics that are dependent on hepatic enzyme activity or drug metabolizing capacity, whereas the kinetics of high extraction drugs are dependent on liver blood flow (141). This can be explained by the following equation for any organ of elimination:

$$\text{clearance (Cl)} = Q \cdot E \quad (6)$$

where Q = organ blood flow and E = extraction ratio.

The effect of protein binding on hepatic clearance depends on the extraction ratio of the drug. For high extraction drugs, where E = 1, Cl must equal Q so that clearance is flow-dependent, because all drug passing through the organ is extracted, whether bound or not. For example, the hepatic extraction ratio of propranolol is about 80%, and propranolol is highly protein bound, having a free fraction of 5–10%. Changes in plasma protein binding thus have little influence on the hepatic clearance of propranolol, because to

have an extraction ratio greater than its free fraction, the drug must be "stripped" from the plasma proteins during its passage through the liver. Most drug passing through the liver, whether bound or not, is removed. Thus, for a high extraction drug, hepatic clearance is flow-dependent and is independent of the extent of protein binding.
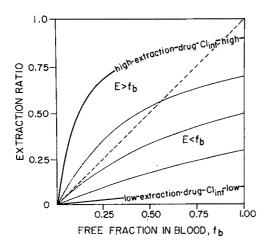
On the other hand, for a drug with a low extraction ratio, such as warfarin, the extent of protein binding limits hepatic clearance. If a drug has a low hepatic extraction ratio and is highly protein bound, hepatic clearance becomes capacity limited and binding sensitive. Changes in binding alter the amount of free drug available for hepatic clearance, because the extraction ratio is smaller than the free fraction in this situation. If a drug has a low hepatic extraction ratio and is not highly protein bound (high free fraction), then hepatic clearance is capacity-limited and binding-insensitive.

Two different types of elimination therefore have been described: one is restricted or limited to the free concentration of drug, i.e., restrictive elimination; the other is nonrestrictive in that free and bound drug can both be removed by the liver, i.e., nonrestrictive elimination. Restrictive elimination is observed when the hepatic extraction ratio is less than the free fraction, and nonrestrictive elimination is observed when the extraction ratio is greater than the free fraction. Examples of highly bound drugs that are restrictively cleared by the liver include phenytoin, valproic acid, and diazepam; examples of drugs that exhibit nonrestrictive elimination by the liver include propranolol and lidocaine. For a drug that is completely eliminated by the liver,

$$Q \cdot E = Cl_H = \frac{Qf_b Cl_{int}^f}{Q + f_b Cl_{int}^f} \quad (7)$$

where f_b = free fraction in drug in blood, Q = hepatic blood flow, Cl_{int}^f = intrinsic clearance of free drug, and Cl_H = hepatic clearance.

Figure 9 shows the relationship between hepatic extraction ratio and changes in protein binding. The dotted line indicates when the extraction ratio (E) = f_b and therefore distinguishes restrictive from nonrestrictive elimination. It can be seen that below the dotted line, elimination is restrictive throughout the whole range of binding, because E is always less than f_b, and Cl_{int} is less than Q. When Cl_{int} exceeds Q, the extraction, and therefore the clearance, becomes nonrestrictive at some stage as binding is increased. Finally, for high clearance drugs when the intrinsic metabolizing capacity (Cl_{int}) is large in comparison to the rate of drug presented to the liver, so that clearance approximates liver blood flow ($Cl_{int} >> Q$ and Cl_H =

Figure 9. The relationship between hepatic extraction ratio (E) and free fraction of drug (f_b). Above the dashed line where $E = f_b$ nonrestrictive elimination occurs, and below this line restrictive elimination occurs. The individual curves represent different values of Cl_{int}/Q corresponding to stepwise changes in extraction when $f_b = 1$. (Modified from reference 141 with permission.)

Q), the free fraction does not affect extraction or clearance until f_b becomes very small, less than 0.25 in Figure 9. Following the upper curve in Figure 9, which represents a drug with a high E and high Cl_{int}, it can be seen that extraction changes very little over a wide range of binding, but as the free fraction becomes very small, there is a steep change in hepatic extraction. However, in the case of the lower curve in Figure 9, which represents a low extraction drug with low Cl_{int}, there is an approximately linear relationship between extraction ratio and free fraction.

Renal Clearance

From general principles (Cl = Q·E), drugs that are highly cleared or extracted by the kidney have renal clearance values which approximate renal blood flow, are flow-dependent, and are relatively insensitive to changes in protein binding. In contrast, for low extraction drugs, renal clearance is sensitive to changes in protein binding.

Drugs may undergo glomerular filtration, active secretion, and/or reabsorption. Drugs that are only filtered yield a glomerular filtrate which is an ultra-filtrate,

$$\text{Renal Clearance } (Cl_R) = f_u \times GFR \qquad (8)$$

where f_u = unbound fraction of drug in plasma and GFR = glomerular filtration rate.

Because albumin does not pass through the glomerular membrane, drug that is bound to albumin cannot be filtered, and only the free fraction is available for glomerular filtration. Therefore, the rate of

glomerular filtration of a drug is inversely proportional to the degree of protein drug binding. Drugs that are principally eliminated by glomerular filtration and in addition are highly protein bound have very long elimination half-lives.

Only free drug is actively secreted by the renal tubules. To maintain the equilibrium between free and bound drug, a decrease in free drug concentration results in dissociation of the protein–drug complex to liberate more free drug, which is then available for tubular secretion. In a fashion analogous to that discussed above for hepatic extraction, this process can be rapid enough to result in an extraction ratio that exceeds the free fraction, implying that drug is being stripped from protein during its passage through the kidney. An example of this situation is seen with penicillin, which, though highly protein bound, has a high renal clearance due to its extensive tubular secretion and minimal reabsorption. Because its renal clearance is unaffected by extent of protein binding, its renal clearance is nonrestrictive.

Renal clearance is reduced by the process of reabsorption from the renal tubules. Extensive reabsorption will reduce the extraction ratio to make a drug one of low extraction. If a constant fraction of the drug entering the tubular lumen is reabsorbed (F_R) and no secretion occurs, then (118)

$$Cl_R = f_u \times GFR \, (1 - F_R). \qquad (9)$$

This equation indicates that renal clearance is still directly proportional to free fraction.

Digitoxin is highly bound to albumin but has low renal clearance due to extensive tubular reabsorption. However, renal clearance is directly proportional to the unbound fraction of digitoxin in an isolated perfused rat preparation in keeping with the above relationship (62).

Effect of Binding on Drug Pharmacodynamics

Although the effects of binding on pharmacokinetics have been extensively investigated (22,28,43, 56,120,122,140), the effect of binding on pharmacodynamics is a relatively unexplored area. Obviously, the effects of binding on drug distribution, half-life, and clearance alter the drug concentration–time relationship and so alter pharmacologic effect at any given time.

Only free drug can diffuse across cell membranes and reach the site of action, and, therefore, pharmacologic effect is dependent on free drug concentration. For most drugs, the area under the free drug plasma concentration vs time curve (AUC_{free}) is,

therefore, related to pharmacologic or pharmacodynamic effect. When high clearance drugs are administered intravenously, AUC_{free} is directly proportional to the free fraction (141). Therefore, increased binding decreases the AUC_{free} and, hence, decreases pharmacologic effect (see next section). After oral administration, AUC_{free} is dependent solely on intrinsic clearance by the liver and is independent of binding changes (141). Therefore, when a high clearance drug is administered orally, binding changes do not affect pharmacologic effect.

Changes in binding are only clinically important for drugs highly bound to plasma constituents. Small increases in the free fraction of highly protein bound drugs produce significant changes in free concentration. A reduction in binding from 95 to 90% represents a 100% increase in unbound fraction of drug. However, for drugs with low plasma binding, the same absolute reduction in binding, from 20 to 15% for example, represents a proportionally smaller (6%) increase in the free fraction.

Although pharmacokinetic characteristics are relatively easy to determine, the relationship between free drug concentration and pharmacologic effect is a particularly difficult one to investigate, and there have been few definitive studies. The importance of the clinical measurement of plasma binding, and interest in the area of plasma drug binding per se, stem from the fact that it is the unbound moiety that has pharmacologic activity. In renal failure, the plasma binding of phenytoin is reduced and the free fraction increased, resulting in an increased pharmacologic effect (10). Because of the higher free fraction, suppression of seizure activity occurs at lower total drug concentrations, and toxicity occurs at total concentrations that, in patients with normal renal function, would be considered to be within the normal therapeutic range. Another example of the relationship between free fraction and effect is seen with propranolol, where the correlation between free propranolol concentration and effect is better than the correlation between total propranolol concentration and effect (79).

The relationship between pharmacodynamic activity and plasma binding of drugs that cross the blood–brain barrier to enter the central nervous system is a complex one. It has long been recognized that drug binding to plasma proteins limits passage of drug across the blood–brain barrier, and that only the unbound moiety, i.e., free fraction, is available for transport into the tissues of the central nervous system—the "free drug" hypothesis. However, recent evidence suggests that the amount of propranolol and lidocaine entering the brain is not restricted to the free moiety (96), and that drug or hormone

bound to protein may enter the central nervous system (95). Uptake of the benzodiazepines into the central nervous system is also greater than one would predict on the basis of the "free drug" hypothesis (68). These findings indicate that the conventional concept limiting drug passage across the blood–brain barrier to the unbound fraction may be overly simplistic, and the area of brain drug uptake and plasma binding is currently one of intensive investigation. However, despite these recent findings, Ghoneim et al. found that in uremic rats thiopental binding is decreased even though total plasma protein and albumin concentrations are normal, and that the reduced binding led to accelerated distribution and increased drug concentrations in the brain and heart (53). They speculated that the reduction in plasma binding of thiopental would prolong the hypnotic and cardiovascular effects of thiopental, in keeping with the reported increase in the hypnotic effects of barbiturates in uremic patients (37). A significant correlation has been found between the time required for induction of anesthesia and serum albumin concentration for the intravenous anesthetic midazolam (109). Midazolam is highly protein bound, and it is postulated that low serum albumin concentrations lead to a higher free fraction and, therefore, more free drug is available to produce central nervous system effects resulting in a more rapid anesthesia induction. It is interesting that a preliminary report suggests that patients receiving bupivacaine by epidural injection who develop central nervous system toxicity have higher free serum bupivacaine concentrations (and lower AAG concentrations) than a group of patients not developing central nervous system side effects, in spite of similar total serum bupivacaine concentrations in both groups (33). This may be due to a protective effect of elevated AAG concentrations, reducing the free fraction of bupivacaine and thereby limiting bupivacaine central nervous system effect.

Displacement Interactions and Toxicity

Drugs may interact adversely to cause toxicity or reduce therapeutic efficacy. Concomitantly administered drugs or endogenous substances can compete with one another for binding sites on albumin, on other serum proteins or on tissue proteins and so result in displacement interactions (80,82). Reduced protein binding or displacement of plasma bound drug may increase drug effect, but in addition alterations in drug disposition occur in parallel, which may make the situation considerably more complex. Concomitant administration of a second drug may cause displacement of the first drug from its binding site, but
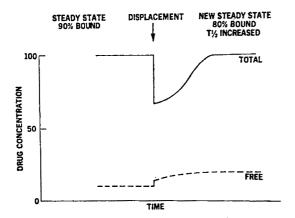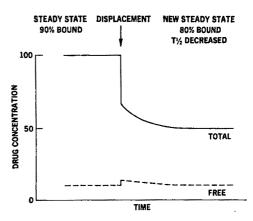
Figure 10. Effect of displacement from protein binding sites on total (—) and free (————) plasma concentrations of a drug whose elimination is not restricted by protein binding. After displacement, the free fraction of the drug doubles, allowing more drug to be distributed outside the plasma space causing the total concentration to decrease. However, with continued administration, because clearance is unaffected by protein binding (nonrestrictive elimination), the total concentration returns to predisplacement levels. This, coupled with the increased free fraction, results in an increase in the free concentration of drug in plasma. (Reproduced from reference 88 with permission.)

Figure 11. The effect of displacement from protein binding sites on the total (—) and free (————) plasma concentrations of a drug whose elimination is restricted by protein binding (low extraction). After displacement, the free fraction of drug doubles, allowing more drug to be distributed outside the plasma space causing the total plasma concentration to decrease. However, in contrast to Figure 10, with continued administration, the higher free fraction results in an increased clearance (restrictive elimination) so that the total concentration decreases and the free concentration has decreased to one-half. (Reproduced from reference 88 with permission.)

the concentration of the displacing drug must approach the molar concentration of the sites on the binding protein so it reduces the sites available for binding. Any endogenous or exogenous substance that exhibits concentration-dependent binding (increase in the unbound fraction with increased concentration) at therapeutic concentrations will cause displacement of drugs that bind to the same site because it is already able to saturate its own binding sites. Therefore, salicylate, phenylbutazone, and the sulfonamides are commonly reported to displace albumin-bound drugs.

The pharmacologic effect of displacement of one drug from its binding sites by another drug depends on whether the drug being displaced undergoes restrictive or nonrestrictive elimination (Figs. 10, 11) (88). For a low extraction drug the elimination of which is restricted by protein binding, if the free fraction is suddenly increased by a displacement interaction, the resultant increase in the free concentration causes drug to leave the plasma space. This leads to an increased volume of distribution and, therefore, a decrease in total plasma drug concentration, because there is now a larger "box" for the drug to distribute in. With continued administration, and reestablishment of a new steady state, the total concentration will tend to recover; however, clearance is also increased by the increase in free fraction because the clearance of a low extraction drug is dependent on the free fraction (see Effect of Binding on Drug Disposition). This increase in clearance restores the free concentration to predis-

placement levels while the total drug concentration decreases. Therefore, after reestablishment of steady state after the displacement reaction, the free fraction is higher, but the total concentration is reduced so that there is no change in free concentration and, therefore, no long term change in pharmacologic effect or toxicity (Fig. 10). However, with high extraction drugs, clearance is independent of protein binding (see Effect of Binding on Drug Disposition) so that when the free fraction increases due to displacement, there is a decrease in total concentration due to an increase in volume of distribution, but with continued administration the total concentration eventually returns to its predisplacement level because clearance remains unchanged. The increase in free fraction causes an increase in free concentration that continues, and therefore the possibility of increased pharmacologic effect and toxicity exists (Fig. 11).

The practical importance of displacement interactions depends on such factors as the extent of protein binding, the hepatic extraction ratio, and the therapeutic ratio. Drugs which would be likely to be involved in clinically important displacement interactions would, therefore, be highly plasma bound (>85%), have a small volume of distribution, and show a narrow range of therapeutic concentrations.

Many displacement interactions have been described for the low extraction restrictively eliminated drug, warfarin. Warfarin is highly bound to albumin, and displacement interactions have been reported with chloral hydrate, clofibrate, and phenylbutazone (73,74).

A displacement interaction between sulfaphenazole and the low extraction drug tolbutamide may play a role in the potentiation of tolbutamide-induced hypoglycemia (21). It has been suggested that the administration of sulfafurazole may enhance thiopental anesthesia due to competitive displacement of thiopental from binding sites on plasma proteins (25). For some of these displacement interactions, however, other mechanisms, such as alterations in drug metabolism, may contribute to the altered toxicity.

The local anesthetic bupivacaine is highly bound to plasma proteins (31,32) and has a low therapeutic ratio (84), indicating that displacement interactions might result in toxicity. Diphenylhydantion, quinidine, meperidine, and desipramine displace bupivacaine in vitro (51), whereas diazepam has no effect (51); whether these findings can be extrapolated to the in vivo situation has been questioned (132). Bupivacaine displaces mepivacaine in vitro (63), indicating that displacement interactions may occur between amide local anesthetics.

Conclusions

Physicians recognize that for many drugs there is a close relationship between plasma total concentration and effect. However, for drugs that are highly plasma bound, effect (be it therapeutic or toxic) may be principally dependent on free concentration, so that an understanding of the factors influencing drug binding to plasma is critical to the intelligent interpretation of drug concentration–effect relationships.

The plasma binding of many drugs may decrease or increase due to a variety of pathophysiologic factors, with resulting important pharmacokinetic and pharmacodynamic consequences. Measurement in plasma or blood of total drug concentrations alone may be misleading and lead either to an inappropriate increase in therapy which might be potentially hazardous, or to the initiation of subtherapeutic dosages. These, as well as practical methodologic problems, are obstacles to the emergence of the routine monitoring of free drug concentrations as a guide to therapy.

Appendix

Protein Plasma Binding of Some Important Anesthetic Drugs

Drug	% Bound	References
Alcuronium	40	102
Alfentanil	92	87
Atropine	39	75
Bupivacaine	95	131
Etidocaine	95	131
Etomidate	71–75	17,106
Fazadinium	51	38
Fentanyl	84	87
Gallamine	low	124
Ketamine	26	29
Lidocaine	60–80	100,146,131,112
Lofentanil	94	87
Meperidine	42–60	76,66,133
Mepivacaine	80	131
Metocurine	32–35	146,86
Methohexital	73	14
Midazolam	94	2
Morphine	35	93
Pancuronium	11–29	145,38
Sufentanil	92	87
Thiopental	80–84	16,89
Tubocurarine	43–51	146,134,86
Vecuronium	30	38

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Technical Communication

A Clinical Comparison of Transcutaneous PO_2 and Pulse Oximetry in the Operating Room

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The early detection of hypoxia during anesthesia is one of the most important goals of intraoperative monitoring. Sequential arterial blood gas measurements can detect hypoxemia, but they are invasive, expensive, and do not provide continuous data. Transcutaneous PO_2 measurement and pulse oximetry are two noninvasive techniques for assessment of oxygenation of tissue and blood, respectively. Although these two techniques are based upon entirely different principles and measure different variables, they are often compared to determine which is the better monitor of patient oxygenation. Neither technique measures the arterial blood oxygen tension, but both techniques are continuous and noninvasive.

In the present study, measurements of transcutaneous oxygen tension ($PtcO_2$) and pulse oximetric oxygen saturation ($NSaO_2$) are compared with arterial blood oxygen tension (PaO_2) and saturation (SaO_2) determined from radial artery blood samples. Data were obtained intraoperatively and postoperatively from patients undergoing various types surgical procedures. A previous study by Knill et al. obtained similar data in anesthetized healthy patients (1). In Knill's study, the fraction of inspired oxygen (FI_{O_2}) was varied in such a way as to produce end-tidal oxygen concentrations ranging from 6 to 20%. For these hypoxic gas mixtures, the authors found that $NSaO_2$ had a higher correlation with SaO_2 than did $PtcO_2$ with PaO_2. The goal of the present study is to determine these correlations within the range of FI_{O_2} relevant to clinical anesthesia, that is, from 0.21 to 1.0. Our study also includes results for less healthy patients (ASA

class II–IV) and addresses the effect of physical status upon the variables discussed above.

Methods
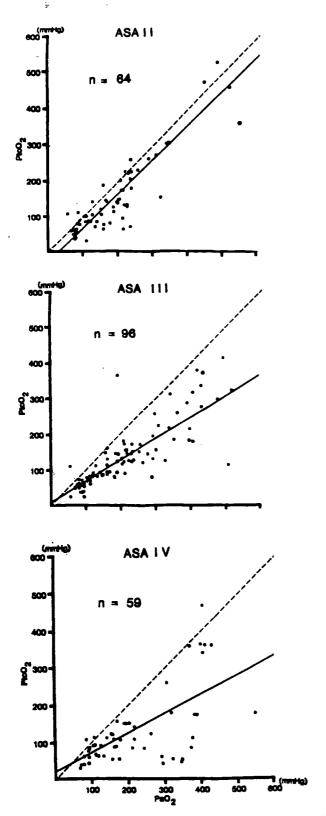
Approval from the university Human Subjects Review Committee was obtained for this study. Patients in whom radial artery catheters were required for any type of anesthesia or surgery were selected for the study. ASA classes II through IV were represented. Upon entering the operating room, each patient had a Novametrix model 807 transcutaneous PO_2 probe placed on the upper chest, and a Biox model III pulse oximeter probe placed on the earlobe. The probes were applied and calibrated as per the manufacturers' recommendations. Ten minutes were allowed for equilibration of the $PtcO_2$ probe at a temperature of 44°C before any measurements were made.

Each measured data set included the following: time, vital signs, $PtcO_2$, $NSaO_2$, and a complete arterial blood gas with O_2 saturation. Arterial blood samples were collected anaerobically in 3-ml heparinized syringes, and were analyzed for blood gases and pH by a Radiometer ABL-2 Blood Gas Laboratory. SaO_2 was determined by an Instrumentation Laboratories IL-282 Co-Oximeter. The first data set was recorded before preoxygenation, at an FI_{O_2} of 0.21. The second set was recorded shortly after endotracheal intubation, at an FI_{O_2} of 1.0. A third set was recorded approximately 10 min after the introduction of nitrous oxide if the latter was used. Additional data were recorded after all changes in FI_{O_2}, or whenever the anesthetist desired an arterial blood gas measurement for any reason. The conduct of the anesthetic was not altered for the purposes of the study.

The data were separated according to ASA groups and analyzed in the following way. Mean values and standard deviations of the four variables ($PtcO_2$, PaO_2,

Figure 1. PtcO₂ vs PaO₂ for ASA class II, III, and IV patients. Solid lines determined by linear regression. Dashes show lines of identity. See Table 1 for linear regression slopes and intercepts. Correlation coefficients: 0.89 for ASA II, 0.82 for ASA III, and 0.66 for ASA IV.

NSaO₂, and SaO₂) were computed. A linear regression relationship was computed for PtcO₂ vs PaO₂, and for NSaO₂ vs SaO₂. Linear regression provides an equation for the least-mean-square best fit straight line relating two variables. Correlation coefficients, expressing the degree to which the variables are related, were also calculated for each pair of variables. The standard error of the estimate for the prediction of SaO₂ from NSaO₂ was also computed. This is simply a root-mean-square deviation of the SaO₂ values from the linear regression line. The PtcO₂ index, defined as the ratio of PtcO₂ to PaO₂, was calculated. This index reflects changes in the relationship between central and peripheral oxygenation that occur with changing peripheral perfusion.
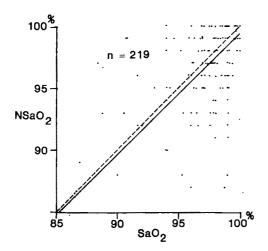
Results

Fifty-five patients entered the study. Twelve were ASA class II, 26 were ASA class III, and 17 were ASA class IV. There were a total of 64 data sets from ASA class II patients, 96 from ASA class III, and 59 from ASA class IV. Figure 1 shows transcutaneous P_{O_2} plotted vs simultaneous measurements of PaO₂ for ASA groups II, III, and IV. The linear regression straight line and the line of identity are shown for each group. Figure 2 shows a similar plot of NSaO₂ vs SaO₂ values obtained at the same times as the data in Figure 1. In Figure 2, the data from all three ASA groups are shown in one plot, because there is no significant difference between groups in these data.

Table 1 shows the results of the statistical analysis of the data. Note that for PtcO₂ vs PaO₂, a correlation of 0.89 is obtained for the ASA class II group. A similarly high correlation of PtcO₂ with PaO₂ has been found in previous intraoperative studies (2). However, in the present study this correlation decreases to 0.82 and 0.66 for the ASA class III and IV groups, respectively. In addition, the slope of the linear regression relation decreases from 0.89 for the ASA II to 0.53 for the ASA IV group. Consequently, the PtcO₂ index also decreases from 0.78 for ASA II patients to 0.63 for ASA IV patients. The PtcO₂ index is not identical to the linear regression slope because of the nonzero y-intercept of the linear regression line.

On the other hand, the correlation of NSaO₂ (pulse oximeter) vs SaO₂ is 0.60, 0.59, and 0.49 for the three ASA groups, and the linear regression slopes are 0.72, 0.61, and 0.66, respectively. These correlations are lower than those for PtcO₂ vs PaO₂, but are significant ($P < 0.01$). There is less variation in the correlation coefficient and regression line slope among the ASA groups for the SaO₂-NSaO₂ relationship.

An example of the use of noninvasive monitoring for the detection of impending hypoxemia is shown

Figure 2. $NSaO_2$ vs SaO_2 with all patients shown on one plot. There were no significant differences between ASA groups. Lines determined as in Figure 1 (see Table 1). Correlation coefficients: 0.60 for ASA II, 0.59 for ASA III, and 0.49 for ASA IV.

Table 1. Statistical Analysis of $PtcO_2$ and $NSaO_2$ Data

	ASA II	ASA III	ASA IV
$PtcO_2$ vs PaO_2			
n	64	96	59
$PtcO_2$[a]	149 ± 105	136 ± 88	120 ± 102
PaO_2[a]	190 ± 105	207 ± 120	203 ± 127
r value	0.89	0.82	0.66
Slope	0.89	0.60	0.53
Intercept	19	12	13
$PtcO_2$ index[a]	0.78 ± 0.27	0.68 ± 0.28	0.63 ± 0.28
$NSaO_2$ vs SaO_2			
n	64	96	59
$NSaO_2$[a]	96.7 ± 3.5	97.4 ± 3.0	96.6 ± 3.1
SaO_2[a]	97.5 ± 2.9	97.7 ± 2.9	97.7 ± 2.3
r value	0.60	0.59	0.49
Slope	0.72	0.61	0.66
Intercept	26	38	32
SEE %	2.84	2.46	2.74

Slope and intercept are for linear regression best-fit line.
SEE, standard error of the estimate.
[a]Mean ± SD.

in Figure 3. Note that in this case large variations in PaO_2 and $PtcO_2$ occurred without a change in SaO_2 and $NSaO_2$ (Fig. 3). The $PtcO_2$ decreased from 450 to 100 mm Hg during a period in which the $NSaO_2$ did not change. Most of this decrease was the result of reducing FI_{O_2} by the addition of nitrous oxide. The remainder is attributed to an increased intrapulmonary shunt in a prone patient. As the case continued, the $PtcO_2$ dropped further to 47 mm Hg, with a corresponding PaO_2 of 56 mm Hg. At this point, the $NSaO_2$ from the pulse oximeter fell to less than 90%, thus warning of impending danger to the patient.

Discussion

This clinical study demonstrates a higher correlation between $PtcO_2$ and PaO_2 than between $NSaO_2$ and SaO_2. A previous comparison of these two noninvasive monitors in human volunteers obtained the opposite result (1). The reason for this discrepancy is that the correlation coefficient is sensitive to the FI_{O_2} range over which the data are collected. Knill et al. presented data for FI_{O_2} less than 0.25, whereas in this study FI_{O_2} was varied from 0.21 to 1.0, which is the usual range encountered during anesthesia and critical care. The hypoxic gas mixtures used by Knill et al. produced a wider range of $NSaO_2$ and thus a better correlation with SaO_2. Our study is "biased" in the opposite direction. The wider range of FI_{O_2} in this study produced a correspondingly wider range of PaO_2 and $PtcO_2$, which in turn leads to a higher correlation between these two variables. Obviously, the correlation coefficient by itself can be misleading when not considered in the context of the design of the experiment.

The high correlation between $PtcO_2$ and PaO_2 in the healthier adult patients of this study (ASA class II) confirms the findings of previous investigators. Four studies within the past few years, involving more than 1500 data sets, found r values between 0.89 and 0.97 (2-5). All patients in these previous studies were considered hemodynamically stable.

It is interesting that the $PtcO_2$ index decreases significantly with worsening physical status. This decrease quantifies the poor peripheral oxygenation that is present in many high risk patients, particularly those with low cardiac output (3,6,7). This phenomenon is another expression of the fact that transcutaneous P_{O_2} is a measurement of oxygen delivery to peripheral tissues, rather than oxygenation of the blood. In contrast, the pulse oximeter data have a standard error of the estimate (SEE) that does not vary appreciably with patient physical status. This is a result of the fact that the pulse oximeter is designed to be insensitive to local perfusion or blood volume. It accomplishes this by varying the intensity of its light source to obtain a stable "pulse added" absorbance signal. This absorbance signal is then empirically correlated to SaO_2 using a relationship that was developed in healthy volunteers (8). $NSaO_2$ is thus sensitive only to SaO_2 and not to oxygen delivery.

Conclusions

Attempts to compare the "accuracy" of transcutaneous P_{O_2} with that of pulse oximetry are misleading, because the two techniques do not measure the same variable. The accuracy of the pulse oximeter in determining the arterial hemoglobin saturation has been determined previously in healthy volunteers, using a
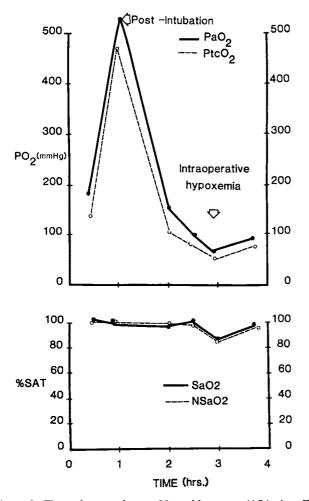
Figure 3. These data are from a 28-yr-old woman (ASA class II) undergoing a cervical laminectomy. Note the wide ranges of $PtcO_2$ and PaO_2 values and the close correlation between the two ($PtcO_2$ index = 0.80 ± 0.08). While the $PtcO_2$ decreased from 460 to 86 mm Hg, the $NSaO_2$ showed no significant change. (Most of this decrease was a result of the addition of nitrous oxide to the gas mixture; the remainder can only be explained by an increased intrapulmonary shunt.) When $PtcO_2$ decreased further to 47 mm Hg, the $NSaO_2$ fell to 84%, a significant decrease. At this point, the PaO_2 was 57 mm Hg.

saturation range of 70–100% (8). On comparing $NSaO_2$ with saturations measured in arterial blood specimens, we found a correlation of 0.98. The "accuracy" of $PtcO_2$ measurements with a heated Clark electrode is a more difficult quantity to define, because $PtcO_2$ is in fact a new variable. It is not the same as PaO_2, and the inequality of these two quantities should not be interpreted as an "inaccuracy" of transcutaneous measurements. Because $PtcO_2$ measures oxygen tension at the skin surface, it will decrease in states of low cardiac output as well as low blood oxygenation. This may be viewed as an advantage of the technique, since it will warn of decreases in either arterial oxygenation or tissue perfusion.

The results of this study are an indication of what the anesthesiologist can expect in routine intraoperative monitoring by these two noninvasive techniques. FI_{O_2} is never intentionally made less than that of room air during anesthesia, and in the clinically applicable range of FI_{O_2} most patients will maintain an arterial hemoglobin saturation of greater than 95%. Exceptions will occur in cases of airway mismanagement (esophageal intubation, ventilator disconnect, etc.) or large physiologic shunts, and the pulse oximeter will be helpful in detecting these events. However, the PaO_2 must drop to less than 70 mm Hg before significant desaturation will occur, and the pulse oximeter will not warn of downward trends in PaO_2 over the wide range of oxygen tensions above this level (Fig. 3). The transcutaneous oxygen electrode will detect changes in PaO_2 over its entire range. It also responds to changes in skin perfusion; this dependence upon two physiologic variables makes the interpretation of $PtcO_2$ during anesthesia more difficult, particularly for those not accustomed to its use. The transcutaneous electrode also requires a 10-min warm-up period after probe placement, and calibration to room air prior to each use.

In conclusion, pulse oximetry and transcutaneous oxygen measurement are both useful noninvasive monitors of oxygenation during anesthesia. They measure different variables, and each has its own set of advantages and disadvantages. The choice between the two monitors should be made on a case-by-case basis, which suggests that anesthesiologists should become familiar with both techniques.

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Clinical Reports

Ketanserin in the Preoperative and Intraoperative Management of a Patient with Carcinoid Tumor Undergoing Tricuspid Valve Replacement

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Carcinoid tumors originating from enterochromaffin cells in intestines, bronchus, and stomach have been associated with fatal cardiovascular and respiratory complications mainly caused by the release of serotonin (5-hydroxytryptamine), vasoactive substances, histamine, and bradykinin (1). Fibrous tissue deposition in the tricuspid and pulmonary valve may also occur. Preoperative preparation of these patients usually includes the use of antiserotonin medication (2–5). Ketanserin is a competitive serotonin receptor blocker that has been previously used to treat hypertension after coronary artery bypass surgery (6). We describe treatment with ketanserin of a case of severe hypertension during cardiopulmonary bypass in a patient with metastatic carcinoid undergoing tricuspid valve replacement.

Case Report

A 46-yr-old woman with a history of a small bowel carcinoid resected 16 yr ago was admitted with a diagnosis of tricuspid and pulmonary insufficiency. Over the past 9 yr she developed carcinoid syndrome with progressively worsening symptoms (diarrhea and flushing). During the past 2 yr, she developed progressive right heart failure with increasing shortness of breath and peripheral edema that responded to

furosemide and digoxin. Cardiac catheterization revealed severe tricuspid insufficiency and moderate pulmonary stenosis and regurgitation. She was scheduled for tricuspid valve replacement and pulmonary valvulotomy.

Medical history included stress diabetes during pregnancy and allergies to various medications and foods. Current medications were ketanserin, 20 mg twice a day, for 8 days plus digoxin, 0.25 mg, and furosemide, 40 mg daily.
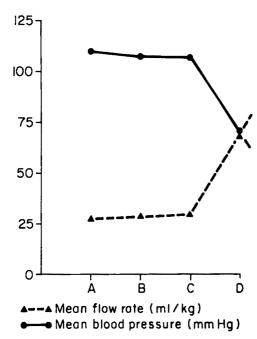
Physical examination revealed a 105-lb woman, flushed and comfortable only in upright position. Blood pressure was 85–90/70 mm Hg with a pulse rate of 75. Lungs were clear. There was a III/VI systolic murmur at left sternal border. Abdominal examination revealed hepatomegaly (2 finger breaths below right costal margin).

Admission laboratory data and chest x-ray were within normal limits. The electrocardiogram (ECG) showed an incomplete right branch bundle block (RBBB). Premedication consisted of oral lorazepam, 4 mg, 1 hr prior to anesthesia.

On arrival in the operating room, a 14-gauge intravenous catheter and a 20-gauge radial artery catheter were inserted. A slow, smooth induction of anesthesia was performed using lorazepam, 8 mg, fentanyl, 25 μg/kg, and pancuronium. Tracheal intubation was performed after intravenous administration of lidocaine, 1.5 mg/kg, and methylprednisolone, 1 g. A right internal jugular central venous pressure (CVP) catheter was then inserted. The initial CVP, 19 mm Hg, remained unchanged until cardiopulmonary bypass (CPB). Anesthesia was maintained prior to CPB with fentanyl plus pancuronium for relaxation. Low

Figure 1. Flow rate (ml/kg) and mean arterial pressure (mm Hg) during cardiopulmonary bypass (CPB). A, no vasodilators; B, sodium nitroprusside; C, sodium nitroprusside plus trimetaphan and diasoxide; and D, ketanserin, 20 mg intravenously.

concentrations of isoflurane were added as necessary. When CPB was instituted, during which time the patient was cooled to 23°C, the flushing slowly disappeared and then gradually worsened to a level greater than that seen before bypass. The patient received 1 g of methylprednisolone at the start of bypass and was given intermittent doses of lorazepam, fentanyl, and pancuronium. Soon after CPB was instituted the patient developed severe hypertension (mean blood pressure, 120 mm Hg) despite using low blood flow averaging 30 ml/kg (Fig. 1). An infusion of sodium nitroprusside (SNP) was started with 75 mg being given over 30 min and blood pressure decreased to 110 mm Hg and the flow rate increased to 32.5 ml/kg. Because at the continuous rate sodium nitroprusside can produce cyanide poisoning, 2 other vasodilators were added without any significant effect: diasoxide, 3 mg/kg as a bolus, and trimetaphan as a continuous infusion (4 mg/kg). Mean arterial blood pressure was 105 mm Hg and the flow rate via cardiopulmonary bypass at this time was 35 ml/kg. At this time ketanserin, 20 mg, was given intravenously with an additional 40 mg 5 min later. Subsequently, there was a rapid decrease of blood pressure from 105 mm Hg (SNP, trimetaphan) to 65 mm Hg and an augmentation of flow rate via the cardiopulmonary bypass to 70 ml/kg that necessitated discontinuation of vasodilator infusions. Blood glucose levels that increased from 120 mg/100 ml to 750 mg/100 ml 30 min after

starting cardiopulmonary bypass necessitated infusion of insulin and potassium. Serum electrolyte levels measured every 15 min during CPB were within normal limits except for mild elevations of potassium. Serum bradykinin levels measured before, during, and after anesthetic induction and cardiopulmonary bypass and 6 hrs later were 1.05, 1.10, 3.75, 1.60, and 1.20 ng/ml, respectively. Cardiopulmonary bypass was terminated without complications except for atrioventricular dissociation that required insertion of pacing wires. An additional gram of methylprednisolone was given after CPB, and the patient's cardiovascular status remained stable while anesthesia was maintained with fentanyl plus pancuronium for relaxation. At the end of the operation, the patient's face and extremities were more edematous than preoperatively. The patient's postoperative course was uneventful except for persistent atrioventricular dissociation that required insertion of a permanent transvenous pacemaker.

Discussion

Carcinoid tumors secrete mainly serotonin and histamine, and usually are accompanied by one or more of the classical symptoms of flushing, diarrhea, wheezing, and valvular lesions in the heart (mainly tricuspid) (1). Carcinoids may also produce melanocyte stimulating hormone, adrenocorticotrophin hormone (ACTH), insulin, glucagon, gastrin, secretion, epinephrine, and testosterone (7). There is an increase in the hydroxylation pathway of tryptophan into hydroxytryptophan and hydroxytryptamine (serotonin). This may result in hypoproteinemia and pellagra in the patients with carcinoids.

Cardiopulmonary bypass is usually associated with release of serotonin (8,9). Serotonin has positive inotropic and chronotropic effects on the myocardium with increases in blood pressure when neurogenic vascular tone is low and decreases in blood pressure when the tone is high (8). These effects may explain the hypertension seen during CPB. Serotonin may also account for the prolonged recovery seen in patients after general anesthesia because serotonin prolongs sleep. The hyperglycemia seen in our patient was mostly caused by serotonin stimulation of glycolysis and glycogenolysis (10,11).

Ketanserin, a quinazoline derivative, is a competitive serotonin (5-hydroxytryptamine) 5-HT$_2$ receptor blocker that has previously been used to treat hypertension after coronary artery bypass surgery (6). According to in vitro and in vivo pharmacologic studies, ketanserin appears to antagonize the vasoconstricting, bronchoconstricting, or platelet-aggregating ef-

fects of serotonin (12). Ketanserin does not antagonize the vasodilator effects of serotonin, nor does it influence the effects of serotonin on gastrointestinal smooth muscle. It also possesses some α-adrenergic blocking properties at concentrations greater than those required to completely inhibit the effects of serotonin. The pharmacologic profile of ketanserin sharply contrasts with that of other serotonin antagonists that either have mixed $5-HT_2$ receptor agonist–antagonist properties or may cause hallucinations (methysergide). The effects of ketanserin are essentially peripheral, not central. Central nervous system side effects do not occur at therapeutic doses of ketanserin.

Ketanserin reduces serotonin-induced hypertension and gastrointestinal motility in a dose-related manner, but clinical responses vary considerably between patients. This variability is because, in addition to serotonin, other mediators, such as bradykinin and histamine, may also be released by carcinoids and cause symptoms. Sodium nitroprusside, trimetaphan, and diasoxide were without significant effects on the blood pressure when given to treat the hypertension that occurred during CPB in our patient (Fig. 1). The hypertension responded only to ketanserin, a serotonin inhibitor.

Ketanserin seems to be an ideal drug to treat hypertensive episodes in patients with carcinoid tumors because of its rapid onset of action and lack of major side effects. It is usually given in doses of 20–40 mg orally twice daily for 8 days prior to surgery. Intravenous injection of 5–10 mg can also be given as needed during the surgery or on the morning of surgery.

In summary, we describe the use of intravenous ketanserin for the rapid and effective control of severe hypertension that occurred during cardiopulmonary bypass in a patient with a carcinoid tumor.

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Low-Dose Intravenous Regional Anesthesia in a Case of Multistaged, Bilateral Hand Surgery

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When both upper limbs have been injured, regional analgesia, though of considerable benefit when only one upper extremity is to be operated upon, may not be feasible. Based on a previously described method of low-dose intravenous technique (LIVRA) (1) we present a new method of intravenous regional anesthesia that allows surgery to be performed on both upper limbs simultaneously or consecutively.

Case Report

A healthy 22-yr-old man was injured in both upper limbs as a result of an explosion. He was seen in the emergency room within an hour and was fully conscious but in pain. Blood pressure was 110/70 mm Hg, and pulse rate was 72 beats/min. The wounds were grossly contaminated. Multiple superficial abrasions and tattoo burns were present. There was a laceration of the skin and extensor tendons of the right hand, with an open fracture of the proximal interphalangeal (PIP) joint of the fifth finger. A complex laceration of the hypothenar area of the left hand was present. The left thumb was lacerated over the distal phalanx.

An intravenous infusion of Hartmann's solution with penicillin and kanamycin was started into a vein on the dorsum of the right foot. Meperidine, 50 mg intravenously, was given for pain. The patient was then transferred to the operating room for cleansing and debridement of wounds. Because he had eaten 1 hr before the injury, it was decided to use bilateral LIVRA with below-elbow tourniquets. Because a double dose of local analgesic drug would be used for bilateral consecutive procedures, an additional tourniquet was applied above the elbow on both sides as a precautionary measure.

First Operation

Blood pressure, pulse, and ECG were monitored; LIVRA was carried out as follows:

1. The above-and-below-elbow bilateral tourniquets were connected to a pressure source but not inflated.
2. An intravenous catheter was inserted into the dorsum of each hand.
3. Exsanguination on the right side was obtained by elevation for 5 min (instead of using an Esmarch bandage) because of the wounds and fractures. After exsanguination, the below-elbow tourniquet was inflated to 300 mm Hg. An Esmarch bandage was then placed between tourniquets to exsanguinate the space between them, followed by inflation of the above-elbow tourniquet to 300 mm Hg. The Esmarch bandage was then removed.
4. After ensuring satisfactory ischemia, 12 ml bupivacaine, 0.5% (60 mg), was injected on the right side through the catheter on the dorsal surface of the hand. All structures distal to the below-elbow tourniquet became progressively anesthetized. After approximately 3–5 min, the below-elbow tourniquet was released to permit the bupivacaine remaining in the veins to reach the level of the above-elbow tourniquet. Anesthesia and paralysis of the hand was complete in 10 min. This permitted the cleansing of all the wounds and removal of foreign bodies from the right forearm and fifth finger.

Thirty-six minutes after commencement of anesthesia the tourniquet was released. Bleeding of the wounds and circulation to the fifth finger were noted to be satisfactory. No further hemostasis was necessary. A sterile dressing was applied to the entire extremity after removal of the distal tourniquet, and a

volar plaster of Paris cast was applied to the fifth finger in the functional position.

We then proceeded to the left hand. The anesthetic procedure used on the right arm was repeated for the left side, with the same dose of bupivacaine used. Exploration showed that the sensory and motor branches of the left ulnar nerve had been contused but not disrupted. Ischemic or necrotic hypothenar muscle tissue was excised. After hemostasis the wound was packed with a wet dressing. A laceration of the soft tissues of the thumb was sutured. As with the right forearm, foreign bodies were removed, and a thorough debridement was done. Reconstruction of the hypothenar muscles was delayed, as well as suturing of skin lacerations.

Analgesia was excellent throughout the whole procedure on both sides. Tourniquet pain was avoided by alternating the inflation of the cuffs every 20 min. After release of tourniquets, the patient was taken to the recovery room where he was observed for 1 hr. Duration of tourniquet ischemia was 36 min on the right side and 52 min on the left. Recovery was uneventful.

Second Operation

One week later, surgical exploration of the wounds was performed using the same bilateral consecutive LIVRA with above-and-below-elbow tourniquets. On this occasion the right side required 12 ml (60 mg) bupivacaine, 0.5%, and the left side 15 ml (75 mg) to obtain anesthesia. The wounds contained foci of necrotic tissue; requiring further debridement of the dorsum of the fifth digit of the right hand and the hypothenar muscles of the left hand. The wounds were repacked with wet dressings and a new supportive plaster of paris cast applied. Again anesthesia was excellent with no side effects. Duration of ischemia was 23 min on the right side and 37 min on the left.

Third Operation

One week later LIVRA was again employed using, consecutively, 15 ml (75 mg) bupivacaine, 0.5%, on the right side, and 12 ml (60 mg) on the left to obtain anesthesia. Wounds were clean, with no sign of infection or necrosis. Through a dorsal approach an arthrodesis was performed on the PIP joint of the right fifth digit. In the left hypothenar area, intrinsic muscles were approximated in layers and the skin sutured. Ischemia lasted 55 min on the right side and

32 min on the left. The postoperative course was uneventful. Wounds healed normally, but hypoesthesia of the left fifth digit persisted.

Fourth Operation

Two weeks later, exploration and neurolysis of the ulnar nerve was performed at left palm level under LIVRA. Fifteen milliliters (75 mg) of bupivacaine, 0.5%, were used. A slit silicone cuff was introduced, isolating the nerve from new adhesions of the hypothenar muscles. Duration of ischemia was 44 min.

Discussion

Prior to the introduction of LIVRA, patients who were candidates for emergency surgery because of bilateral multiple wounds of the upper limbs were subjected to general anesthesia, which often was delayed because the patient had eaten (2,3). Also, anesthetic risk was increased as patients suffering from wounds usually had to be operated upon repeatedly, often with prolonged procedures within short periods of time. Regional anesthesia—brachial plexus block or conventional intravenous regional anesthesia—is often difficult during bilateral surgery of the upper limbs.

Supraclavicular and interscalene blocks entail the danger of complications such as pneumothorax and intravascular or subarachnoid injection of local anesthetic (4). When conventional intravenous regional anesthesia is used, a large volume of anesthetic solution, often 0.5% lidocaine, is injected distal to the arm tourniquet. Conventional intravenous regional anesthesia for both arms needs an even higher volume of local anesthetic solution. However, LIVRA with above-and-below-elbow tourniquets overcomes the above-mentioned problems, provides excellent operative conditions (ischemia and analgesia), and enhances patient safety because of the small amounts of local anesthetic required (5,6). Nonetheless, tourniquet release was done cautiously, always 20 min or more after the local anesthetic injection. We must also stress that surgery was limited to the area below the forearm tourniquet.

The LIVRA technique with bupivacaine provides more prolonged operative and residual postoperative analgesia than does LIVRA using lidocaine by virtue of the protein binding property of bupivacaine (1,7,8). On the other hand, we have used lidocaine for shorter operations that do not necessitate revision of hemostasis and continuation of surgery after tourniquet release.

Arm-forearm tourniquet position has been suggested in the past (9), but has not been emphasized

as a method for lessening the volume and dose of local anesthetic used in intravenous regional anesthesia. Compared to double forearm tourniquets, arm-forearm tourniquets provide a larger surgical field, ensuring at the same time complete ischemia and a double barrier to drug leakage into the systemic circulation. There were no side effects in a series of six hundred unilateral operations performed with LIVRA over the past four years in our hand unit. We did not find a correlation between volume of the upper limb, venous dead space, and the amount of drug necessary to produce anesthesia.

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General Anesthesia for Patients Undergoing Percutaneous Transluminal Coronary Angioplasty during Acute Myocardial Infarction

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Nonsurgical myocardial revascularization using percutaneous transluminal coronary angioplasty (PTCA) and thrombolytic therapy with streptokinase is presently being successfully performed to restore coronary blood flow during acute myocardial infarction (AMI) (1). Maximal salvage of ischemic myocardial tissue necessitates expedient reperfusion (2) as well as prevention of increased metabolic demands prior to reperfusion (3). However, sympathetic overactivity resulting in tachycardia and hypertension frequently occurs during AMI and can contribute to the progression of ischemic injury (4,5). General anesthesia can prevent the pain and anxiety associated with AMI. Furthermore, tracheal intubation may improve ventilation and decrease the risk of pulmonary aspiration of stomach contents in these nonfasting patients who may develop hemodynamic instability during myocardial reperfusion. In view of these potential advantages, we administered general anesthesia to patients during emergency PTCA for AMI, and we now report our initial experience.

Methods

A protocol has been instituted at Duke University Medical Center for performing emergency PTCA during AMI. Criteria for entry into the protocol include onset of ischemic pain within 6 hr of arrival in the cardiac catheterization laboratory and ST segment elevation of 0.2 mV or greater in two or more leads of a 12-lead ECG. Patients receive streptokinase, 1.5 million units intravenously, lidocaine, 225 mg intravenously in divided injections followed by a 2.0 mg/min continuous infusion, and heparin, 10,000 units intravenously. In the interventional cardiac catheterization laboratory, patients undergo urinary bladder catheterization and percutaneous cannulation (8.0 French gauge) of the right femoral artery and vein. After placement of a transvenous right ventricular pacing catheter, diagnostic left ventriculography and coronary arteriography are performed to define global ejection fraction and coronary anatomy. The occluding lesion is crossed by a steerable dilatation catheter after intracoronary administration of nitroglycerin to prevent coronary artery spasm (6). Balloon inflation up to 9 atm for 60–90 sec is used for arterial dilation. Arterial blood pressure (via the femoral arterial catheter sheath) and ECG are monitored during the procedure and one arterial blood sample is drawn between ventriculography and angioplasty for measurement of PaO_2, $PaCO_2$, pH, and base excess. After the procedure, a pulmonary arterial catheter is advanced via the femoral venous sheath. The cardiac specific fraction of creatine phosphokinase (CK-MB) is measured at 6–8 hr intervals for 24 hr.

After informed, written consent, five consecutive patients received general anesthesia for the emergency PTCA protocol. Preoxygenation and administration of fentanyl, 100–150 μg intravenously, and pancuronium, 1.0 mg intravenously, preceded anesthetic induction with etomidate, 0.3 mg/kg intravenously, followed by succinylcholine, 1.5 mg/kg intravenously. Oral endotracheal intubation was accomplished in rapid sequence with cricoid pressure and was followed by placement of an esophageal stethoscope, a nasogastric tube, and a catheter in the bladder. The cardiologist then inserted the vascular cannulae in the right groin and commenced the PTCA procedure. Ventilation was maintained with a Drager Compact (North American Drager, Inc.) anesthesia delivery system using a modified Mapleson D breathing circuit (Bain Breathing Circuit, Kendall Inc.).

Maintenance of anesthesia included nitrous oxide, 50%, and vecuronium, 0.05 mg/kg intravenously, until completion of the diagnostic ventriculography (21 ± 1.4 min after induction), at which time enflurane, 0.3%, was also administered by inhalation. Upon termination of the procedure, neuromuscular blockade was reversed with neostigmine, 2.5 mg intravenously, and glycopyrrolate, 0.6 mg intravenously, and the inhalation anesthetic was discontinued. Return of consciousness was immediately followed by tracheal extubation, after which patients were transported to the coronary care unit. One patient given general anesthesia subsequently developed coronary arterial reocclusion, ischemic pain, and ST segment elevation on the seventh day; this patient underwent a second emergency PTCA procedure with general anesthesia, and this second procedure represents the sixth case.

After six patients given general anesthesia were studied, standard patient management for emergency PTCA was reinstituted. This consisted of nasal cannula oxygen (5 L/min) and morphine, 0-10 mg intravenously, plus local infiltration with lidocaine, 1%, at the femoral cannulation site. An anesthesiologist observed and recorded hemodynamic measurements during the next six consecutive patients who received standard analgesia for emergency PTCA for AMI.

To evaluate patient assessment of the program, all patients were interviewed 24–48 hr after the procedure by a cardiologist not involved in their clinical care. Patients rated their perception of pain during the procedure on a 0–10 scale and their level of anxiety on a 0–10 scale from the general well-being schedule (7). Hemodynamic measurements, arterial blood gas tensions, and complications in the two groups were compared, as were time requirements for femoral vein cannulation, myocardial reperfusion, and completion of the procedure. Hemodynamic and arterial blood gas data were analyzed using the BMDP statistical software program (University of California, Los Angeles, 1983). Within-group comparisons from baseline were analyzed using multiple Student's t-tests with Bonferroni corrections, and between-group data comparisons were analyzed with Hotellings T^2 test. Results are expressed as mean ± standard deviation.

Results

The three women and eight men studied were 55 ± 11.4 years old. Two patients in each group had a history of systemic arterial hypertension, and one in each group had a previous myocardial infarction. Arrival in the catheterization laboratory averaged 158 ± 111 min from onset of continuous chest pain with no significant difference between groups. The times required in minutes from arrival in the catheterization

laboratory to cannulation of the femoral vein (16.7 ± 5.1, 21.7 ± 4.9), myocardial reperfusion (62.2 ± 19.8, 66.2 ± 21.6), and completion of the procedure (149 ± 36.7, 137 ± 46.5) were similar between the anesthetized and awake groups, respectively. There were also no differences in preprocedural ejection fraction (0.43 ± 10, 0.52 ± 15) or left ventricular end diastolic pressure (22 ± 9, 25 ± 4 mm Hg) between the anesthetized and awake groups, respectively. Comparisons of baseline hemodynamic measurements on arrival in the catheterization laboratory were not statistically different; however, the heart rate and blood pressures tended to be higher in the anesthetized group.

Anesthetic induction and intubation did not alter hemodynamic values, but during steady-state anesthesia prior to ventriculography the heart rate and rate–pressure product were significantly below baseline levels and remained reduced throughout the procedure (Fig. 1). Hemodynamic values in the awake group did not change during the procedure (Fig. 1). Hemodynamic measurements were similar between groups except that systolic blood pressure was higher ($P < 0.05$) in the anesthetized group 5 min after extubation. Arterial blood sampled between ventriculography and coronary angioplasty showed the arterial oxygen tension to be higher in the anesthetized group (238 ± 91 vs 65 ± 17 mm Hg, $P < 0.002$), although $PaCO_2$ (40.8 ± 6.6, 37.0 ± 4.1 mm Hg) and pH (7.36 ± 0.02, 7.35 ± 0.05) were similar between the two groups.

Anesthetized patients were intubated without complications 11.5 ± 4.4 min after arrival in the laboratory and extubated 4.5 ± 0.7 min after completion of the procedure. In one anesthetized patient and two awake patients electrical cardioversion was necessary because of ventricular tachycardia during coronary arterial dilation. Three awake, but no anesthetized, patients vomited during the procedure. One anesthetized patient who experienced syncope with emesis prior to arrival in the hospital developed pharyngeal bleeding following nasogastric tube placement. Extubation of this patient was uncomplicated, but subsequent radiologic evidence of a mild pulmonary aspiration in the right upper lobe, unaccompanied by clinical manifestations, appeared and resolved over the next 5 days. No other complications developed in the anesthetized group. One patient in the awake group who required a dopamine infusion, insertion of an intraaortic counterpulsation device, and endotracheal intubation during PTCA died on the sixteenth hospital day from cardiogenic shock. No other complications developed in the awake group. Peak serum CK-MB concentrations (94 ± 120, 117 ± 81 IU/L) and duration of hospitalization (10.8 ± 4.4, 9.5
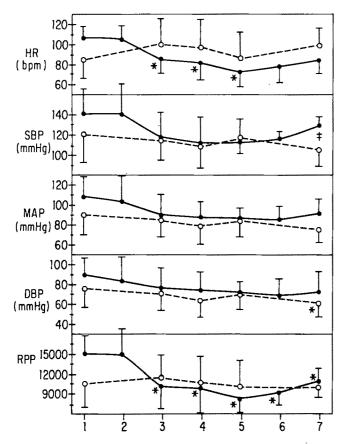
Figure 1. Hemodynamic variables during the angioplasty procedure in the anesthetized (filled circles, solid line) and in the awake group (open circles, dashed line). Measurements are: 1) baseline, i.e., upon arrival in the laboratory and before anesthetic induction; 2) 5 min after tracheal intubation; 3) immediately prior to ventriculography; 4) after ventriculography; 5) at myocardial reperfusion; 6) at extubation; 7) 5 min after extubation, or final measurement in awake group. Abbreviations: HR, heart rate; SBP, systolic arterial blood pressure; MAP, mean arterial blood pressure; DBP, diastolic arterial blood pressure; RPP, rate–pressure product (HR × SBP). *$P < 0.05$ from baseline, ‡$P < 0.05$ between groups.

± 3.4 days) were similar in the anesthetized and awake groups, respectively.

Patient assessments showed that all awake patients were in moderate discomfort (≥5 on a scale of 0–10) throughout the procedure, whereas none of the anesthetized patients had recall of any procedural events. There was a nonsignificant trend towards lower anxiety levels after the procedure among the anesthetized patients (mean 0.6) as compared to awake patients (mean 1.6).

Discussion

This preliminary experience demonstrates that general anesthesia can be safely administered to patients undergoing emergency PTCA during acute myocardial infarction. Anesthesia offers the advantages of complete pain relief, including pain of cardioversion. Furthermore, this anesthetic technique lowers

heart rate–blood pressure product and improves arterial oxygenation that may favorably effect myocardial oxygen supply/demand balance.

Although previous studies have demonstrated the benefits of parenteral analgesia (8) and sedation (9), including inhalation of nitrous oxide (10), the potential therapeutic advantages of general anesthesia during AMI in nonsurgical patients have not been clinically evaluated. Extensive animal research with halogenated inhalational anesthetics has demonstrated an association between an anesthetic-induced reduction in myocardial oxygen requirements and myocardial protection from ischemic injury. When compared to the awake state, anesthetized animals with lower heart rate and mean arterial pressure have a decrease in arrhythmias, mortality and infarction size after coronary artery ligation (11,12). A selective increase in oxygen supply/demand in ischemic myocardium compared to normal myocardium has also been demonstrated with inhalation anesthetics (13,14). Direct myocardial tissue effects might also be important because halothane decreased ST-segment elevation more than similar hemodynamic changes produced by nitroprusside and propranolol (15). However, anesthetic-induced hypotension can also cause detrimental ischemic dysfunction in myocardial tissue supplied by restricted coronary blood flow (16). Therefore anesthetic drug selection and drug dosage is important.

For our protocol, etomidate was used to induce anesthesia because of its rapid onset, brief duration of action and minimal hemodynamic effects in patients with cardiac disease (17). Lidocaine, administered as an antiarrhythmic, also probably attenuated the cardiovascular response to endotracheal intubation. The relatively light level of anesthesia during the procedure was sufficient to reduce heart rate and blood pressure in these nonsurgical patients with high initial sympathetic tone, while also facilitating a rapid emergence and extubation.

Hyperoxic mechanical ventilation, which significantly improved oxygenation in our patients, may be beneficial in ischemic myocardial border zones. A considerable number of acute myocardial infarction patients have arterial hypoxemia (18). Extension of ischemic injury and infarction size has been demonstrated in hypoxemic dogs (19), whereas increased oxygen availability to ischemic border zones decreased ischemia in dogs receiving hyperoxic mixtures (20,21). Furthermore, tracheal intubation may prevent pulmonary aspiration in these patients, many of whom have full stomachs and increased susceptibility to nausea (because of myocardial infarction and injection of radiocontrast material) at the time their mental status is also depressed (because of severe hemodynamic

instability). Three of the six awake patients vomited and two had to be electrically cardioverted from ventricular tachycardia during instrumentation of the coronary artery.

Although no serious anesthetic complications developed in these six cases, administration of general anesthesia for emergency PTCA during AMI is not without potential risks. Potential causes of anesthetic mishaps involve the emergent nature of the procedure, the patient's cardiac disease and preinduction streptokinase therapy. In one patient, posterior pharyngeal bleeding from placement of the nasogastric tube was a potential source for pulmonary aspiration, demonstrating the need for careful instrumentation of the pharynx. Presently, our contraindications for general anesthesia in these patients are the anticipation of difficulty with oral endotracheal intubation and noncardiac disease that would increase anesthetic risk. Bradydysrhythmias and hypotension should be treated prior to anesthetic induction. However, patients with severe hemodynamic instability might require tracheal intubation to prevent aspiration and to normalize ventilation. Finally, because the time from coronary artery occlusion to reperfusion is of utmost importance, anesthesia must not prolong but facilitate the procedure.

This initial experience demonstrates the feasibility of general anesthesia for PTCA during acute myocardial infarction. Although the small number of patients precludes definitive conclusions, we are encouraged by the decrease in heart rate–blood pressure product in the anesthetized group and the fact that anesthesia administration did not increase the time required for reperfusion. The complete relief of pain (including pain of cardioversion) and the enhancement of oxygenation are both advantages of this technique. In view of these preliminary results, randomized clinical studies are in order to test the hypothesis that general anesthesia can augment nonsurgical and pharmacologic salvage of ischemic myocardium during acute myocardial infarction.

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Letters to the Editor

Seizures? Drugs? Timing?

To the Editor:

In responding to Dr. Hymes's report on possible seizure activity during isoflurane anesthesia (1), Dr. Keats correctly notes that electroencephalographic evidence is missing, and the (anecdotal) chance of seizures occuring during emergence from fentanyl is higher than after isoflurane administration (2).

What appears to be even more distressing about the report is the confusion concerning the time frame. In the case report, Hymes notes that induction was facilitated by 100 µg fentanyl. The surgeons commented that the patient was becoming "tight." Approximately 1.5 hr after induction, the patient was again given 100 µg fentanyl. Myoclonus, progressing to seizure developed 30 min later. However, in his discussion, times from administrations of the two boluses of fentanyl until the "event" are listed as 12.75 hr and 1.5 hr, respectively. In light of such disparity in the time reporting, placing credence on the report, anecdotally or otherwise, is probably unwise.

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Anesthesia: A Pragmatic Construct

To the Editor:

For over 100 years, we have searched for the mechanism of general anesthesia. Today, we argue about whether narcotic anesthesia is anesthesia (1,2). We talk about complete and incomplete anesthetics. Why have the answers eluded us?

Perhaps the questions themselves are improper. Perhaps anesthesia is a broad descriptive term, like sickness. We no longer ask what the mechanism of sickness is. We have stopped looking for the perfect medicine (tonic) that cures all ills and makes us well. We have divided sickness into components such as syphilis, anemia, congestive heart failure, etc. We treat each of these conditions and do not expect one drug to cure them all. As we have become more sophisticated, we have subdivided even more. For example, we differentiate an iron deficient microcytic anemia from a macrocytic folate deficient anemia.

I submit the concept that paralysis, unconsciousness, and attenuation of the stress response are the necessary and sufficient components of the anesthetized state. Any drug or combination of drugs that can reversibly provide paralysis, unconsciousness, and attenuation of the stress response can be used in anesthesia. Furthermore, control of these three components *is* general anesthesia.

Paralysis in this construct is defined as the absence of movement or skeletal muscle tone in the operative field. Paralysis can be provided by neural blockade, psychotic reactions, acupuncture, nondepolarizing muscle relaxants, head trauma, and many drugs that affect the central nervous system. This definition of paralysis is peculiar to this construct. Nondepolarizing muscle relaxants are popular for production of paralysis, because the dose necessary easily can be titrated to a specific end point (e.g., train of four), and their effects are readily reversible.

Attenuation of the stress response is a phrase of ignorance. We do not know the nature of stress. We do not know why we feel fatigued at night or after strenuous exercise. Because we do not know all the components of stress or stress response, during general anesthesia we purposefully control only those aspects of stress that we can measure. Usually they are heart rate and systemic blood pressure. Occasionally, we include pulmonary artery pressure and systemic vascular resistance. We do not administer our drugs on the basis of plasma levels of growth hormone, catacholamines, or antidiuretic hormone. Obviously halothane, fentanyl, propranolol, and sodium nitroprusside affect the body in very different ways, yet each has been used to inhibit cardiovascular responses to intubation.

Unconsciousness is not well-defined. It includes amnesia and hypnosis. Unfortunately, we have no universal end point that can serve as a basis for the rational administration of drugs to achieve unconsciousness. The definitions of amnesia and hypnosis are not precise. Does amnesia imply

that information does not get into the brain, or does it get into the brain but not into the memory? Perhaps it is in the memory but cannot be retrieved. Possibly, information regarding intraoperative events is in the subconscious. This information may be retrieved under hyponosis, although it cannot be remembered (3). Like anesthesia, hypnosis and sleep include many different states. The electroencephalographic patterns are different with halothane, enflurane, fentanyl, barbiturates, and benzodiazepine-induced hypnosis. None of these produce normal, physiologic sleep. As a general rule, we administer drugs to affect consciousness without monitoring the effect of these drugs on the level of consciousness. Today we cannot guarantee lack of recall, and we cannot guarantee that intraoperative events and conversations will not affect the patient. The only "monitor" routinely used is the patient's postoperative statement that he or she had no recall. We use a dose of drug that will provide a lack of recall by this monitor in most patients. Recall indicates a failure to anesthetize (4). Presently, the absence of recall is the only objective criterion of unconsciousness-hypnosis-amnesia routinely used. Clearly this is unsatisfactory. Perhaps in the future, something better than processed electroencephalograms will be as routine as nerve stimulators.

Analgesia is not necessary for anesthesia. In order for pain to exist, a conscious brain must interpret impulses from the periphery or within the central nervous system (as in central pain) as pain. By definition, an unconscious individual cannot have pain. On the other hand, a soldier in battle may experience severe injury and nociception without experiencing pain. If there is no pain, analgesia is not necessary. Since analgesia is part of the classic definition of anesthesia, it is important to note here that this departure from the classic definition is not merely semantic. If a patient is having a hysterectomy under epidural anesthesia and if, upon traction of the uterus, heart rate and blood pressure increase, we can ask the patient: "Are you having pain?" In these circumstances the patient may say "No, but I feel nauseated" (personal observation). Many anesthesiologists would administer an antiemetic. Under general anesthesia, the same increases in pulse and pressure coinciding with traction of the uterus may be followed by the administration of fentanyl. Satisfied that the pulse and pressure returned to normal, the anesthesiologist now erroneously concludes that he treated the patient's pain. Upon harvesting organs from brain dead patients, hemodynamic changes may be seen (5,6). Can the dead have pain? Bladder surgery in unanesthetized quadriplegic patients also produces a change in vital signs without pain. These changes in pulse and pressure are signs of a stress response. As long as the stress response is controlled, it matters not what agents are used. The anesthetic contribution of narcotics may reflect their ability to block the stress response by various mechanisms (7,8). The question of whether pain can exist during general anesthesia is a theoretically improper question and a pragmatically useless concept that can lead to improper drug administration.

Paralysis, unconsciousness, and attenuation of the stress response as defined above are the three necessary and sufficient components of anesthesia. As anesthesia has been dissected here, each of the three components of anesthesia beg for dissection in the future. By considering the risks and benefits of each drug's contribution to the three components of anesthesia, we can prescribe the best anesthesia for any patient. No ready-made protocol can fit as well as a good tailor-made anesthetic plan. Such a plan will be easy to manage without unexpected movement, hemodynamic changes, or postoperative psychologic changes. These are the complications that compromise our patients. Absence of these complications is assured by the provision of paralysis, unconsciousness and attenuation of the stress response. This is complete anesthesia.

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Resistance to Pancuronium: Adult Respiratory Distress Syndrome or Phenytoin

To the Editor:

Callanan describes a case of a 15-yr-old, 50-kg girl who developed resistance to pancuronium in the face of adult respiratory distress syndrome (1) and suggests several possible mechanisms for this resistance to neuromuscular blockade. It should be pointed out that one of the medications the patient had been receiving, phenytoin (diphenylhydantoin, Dilantin), has been reported to antagonize neuromuscular blockade. Although anticonvulsants applied acutely to nerve muscle preparation have produced potentiation (2), chronic administration of phenytoin has led to resistance to the effects of neuromuscular blockers (3). In one report (3), the amount of pancuronium needed to effect a predetermined level of blockade increased 46 and 79% in the two patients studied once chronic phenytoin therapy was established. Similar evidence of phenytoin induced re-

their report and their letter to the editor they emphasize the importance of the steel spiral plastic coated catheter in the technique, as well as the importance of failure with the catheter. I have no problem with Bromage's technique, his drug recommendations, his results, or the slight technical variations recommended by Racz and Heavner, with two exceptions. First, we tend to use more concentrated solutions of phenol than Dr. Bromage (10–15% in warm saline), and, second, we have had trouble with the catheter wall integrity of the Racz catheter. The near miss described in my case report coupled with several other leaking catheters have led to the conclusion that potential danger exists despite the precautions suggested.

A recent tragic analogy perhaps is apropos; 25 successful shuttle launches without both a primary and secondary O-ring failure should not have lulled one into thinking that a combined failure would never occur. The "puff of black smoke" in our case was the peculiar pattern of metrizamide leakage from the defective catheter shown in the epidurogram accompanying the case report. I stated that perhaps daily injections should be considered instead of the catheter technique if the latter has a propensity to fail. I, too, rely on chronic epidural catheters (frequently for days) but we must be ever vigilant against the hazards of chronic indwelling catheters. It is reassuring that an improved catheter design is forthcoming, presumably also with a distinctive endorsement. Hopefully, such catheter improvements will reduce the risk of catheter wall failure in such settings.

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Vaporizer Output Increases When Nitrous Oxide Is Eliminated as a Carrier Gas

To the Editor:

I read with interest the report by Scheller and Drummond (1) concerning vaporizer aberrancy caused by nitrous oxide. Although they cite information (2) that was later retracted (3), the report emphasized the importance of understanding changes in vaporizer output concentration that occur while changing carrier gases. Their measurement of residual nitrous oxide in the vaporizer when oxygen replaced it as a carrier gas agrees well with the data reported by Lin (4).

One weakness of their report is that there was no demonstration of a volume change in vaporizer output when nitrous oxide flow was replaced by nitrogen or oxygen. I performed a simple experiment using two Ohio enflurane vaporizers, a Stead–Wells spirometer, and an Engström

Table 1. Vaporizer Output After Replacing Nitrous Oxygen as a Carrier Gas

Time (sec)	Gas collected (ml)	$\dot{V}$(ml/min)	ΔV (ml)
0–20	1420	4260	73
20–40	1405	4215	58
40–60	1365	4095	18
60–120	4095	4095	53
420–640	8085	4042	—

$\dot{V}$, gas flow in ml/min coming from the vaporizer; ΔV, amount of nitrous oxide liberated from the vaporizer after carrier gas change to 100% oxygen.

Emma anesthetic gas analyzer. Vaporizer output concentration was allowed to equilibrate at flows of 4 L/min nitrous oxide, 0.2 L/min oxygen, and 3% enflurane. The carrier gas flow was changed to 4 L/min 100% oxygen. The spirometer was connected to the common gas outlet of the anesthesia machine. Gas flow was measured continuously on Collins spirometer chart paper for 2 min. Five minutes later, after stabilization of enflurane concentration indicated on the Emma, the total gas output was measured for another 2 min.

The results of measurements on two enflurane vaporizers were averaged and are presented in Table 1. Note that 200 ml more gas (nitrous oxide and enflurane) came from the vaporizer in the first 2 min after carrier gas change than was measured coming out during an equal time period 5 min later (ΔV). A decrease in gas flow ($\dot{V}$) with time after replacing nitrous oxide flow through the vaporizer is evident.

These data support previously published reports (5,6) emphasizing the importance of nitrous oxide solubility in volatile anesthetics as a cause of vaporizer aberrancy. When nitrous oxide flow is replaced by oxygen, the nitrous oxide dissolved in the liquid volatile anesthetic in the vaporizer is released and carries anesthetic gases out of the vaporizer, increasing both the concentration of anesthetic and gas volumes coming from the vaporizer. Scheller and Drummond became interested in this phenomenon because fatal anesthetic overdosage occurred in their laboratory animals (1) while changing carrier gases from oxygen/nitrous oxide to oxygen. All anesthetists must therefore understand the consequences of changing carrier gases on vaporizer output.
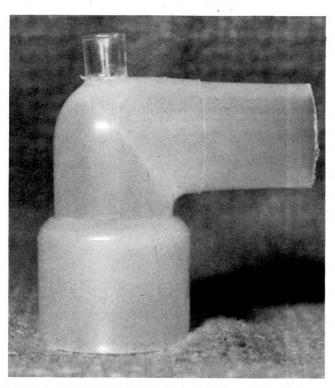
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Figure 1. The clear plastic adapter on this elbow adapter from an anesthetic circuit has been fitted into a predrilled hole.

Figure 2. A plastic remnant from drilling a hole in an elbow adapter is left hanging within the adaptor and could cause an airway obstruction.

Drilling Remnants in Elbow Adapters

To the Editor:

Anesthesia breathing circuits frequently are fitted with gas sampling ports. To accommodate these, on some circuits, an adapter is fitted into a predrilled hole (Fig. 1). On inspection of one of these circuits before anesthetic induction, a long plastic remnant from the drilling process was noted to be hanging within the elbow adapter (Fig. 2). Had the elbow been used, the remnant could have caused partial or total airway occlusion, or, if loosened, could have been aspirated. All such adapters should be inspected prior to use. Presumably, this problem would not occur in circuits in which adapters are molded into place.

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Nail Polish Does Not Affect Pulse Oximeter Saturation

To the Editor:

Often one sees patients wearing nail polish coming for outpatient or emergency anesthesia surgery. One may wish to monitor pulse oximeter saturation on many of these patients, especially when they are having ENT procedures or difficult airway problems. Neither skin pigment nor burned or dirty skin affects pulse oximeter saturations. However, synthetic finger nails do (1). Will nail polish affect the pulse oximeter saturations?
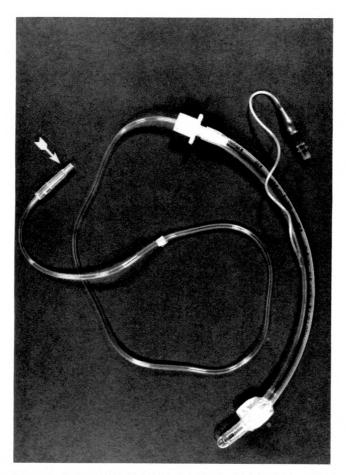
To study this, we gathered 15 volunteers (physicians, nurses, and paramedical personnel) working in the operating room area. Two pulse oximeters (Nellcor) were tested simultaneously. Sensors were applied to the nail beds of the middle finger of both hands of the volunteer. No volunteer was wearing nail polish at this time. Next, the volunteer breathed "blow by" oxygen delivered by corrugated tubing. The oxygen saturation increased in similar fashion with both pulse oximeters.

Then, nail polish was applied to the middle finger of one hand and was left to dry. The above procedure was repeated. Nail polish had no effect on either baseline oxygen saturations or the increase produced by "blow by" oxygen as measured by pulse oximetry.

Bideshwar K. Kataria, MD
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Georgetown University Hospital
Washington, DC 20007

Reference

1. New W Jr. Pulse oximetry. J Clin Monitoring 1985;1:126–9.

Figure 1. Photograph depicting placement of intravenous extension tubing in #7.0 endotracheal tube. The arrow indicates end that can be connected to earpiece adapter or placed in the ear.

A Simple Aid to Blind Tracheal Intubation

To the Editor:

An aid to blind endotracheal intubation using a miniature condenser microphone with amplifier and stereo headphones to amplify breath sounds has been previously described (1). A simple and less expensive method of amplifying breath sounds uses a piece of 30-inch intravenous extension tubing (Abbott Hospitals, Inc., North Chicago, IL) with one end inserted 2–3 cm into the proximal end of an endotracheal tube (Fig. 1), and the other connected to the end of an earpiece adapter or placed directly into the anesthetist's ear. The connector can be cut from the extension tubing to facilitate placement in a smaller endotracheal tube, if necessary. Breath sounds are well amplified, even in the presence of a metal stylet, and the anesthetist can directly observe the patient while performing the intubation.

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Reference

1. Patil VU, Stehling LC, Zauder HL, Chilcoat RT. An aid to blind endotracheal intubation. Anesth Analg 1984;63:882–3.

Respiratory Acidosis after Cardiopulmonary Bypass

To the Editor:

Dr. Robert Sladen (1) ends his paper on "Temperature and Ventilation after Hypothermic Cardiopulmonary Bypass (CPB)" with a question: is the respiratory acidosis seen in the ICU after heart surgery due to changes in deadspace, or to increased CO_2 production? There can be little doubt as to the answer.

The physiologic deadspace fraction, V_Dphys/V_T, during controlled ventilation is unchanged at the end of coronary bypass grafting with hypothermia CPB (2). The respiratory acidosis is therefore caused by an increase in CO_2 production if ventilator settings are unchanged.

In the department of thoracic surgery in Lund, each patient is ventilated by a Servo ventilator coupled to a CO_2 Analyzer 930 (3) during the postoperative period. This system continuously calculates CO_2 production in ml/min, in addition to PET_{CO_2}. It is a common observation that patients who, at the end of surgery, produce 200–250 ml CO_2/min can, 2–4 hr later (the period of maximal temperature increase observed by Dr. Sladen), increase their CO_2 production sometimes to as much as 400–500 ml/min. This is not unreasonable considering the increase in O_2 consumption known to occur during shivering (4).

A second advantage of the system is that one can follow the PET_{CO_2} during this period of metabolic instability. Thus, on admission to the ICU, it might be established that a patient has a $Paco_2$ of 40 mm Hg when PET_{CO_2} is 30 mm Hg. Following this, the ICU team will, at the necessary intervals, change the ventilator setting in order to keep $Paco_2$ and PET_{CO_2} at the same values. Thus ventilation is tailored to metabolic needs. Although the concept of a constant arterial–endtidal Pco_2 gradient does not hold true if large changes are made in ventilator settings (5), it may be acceptable within the context of the ICU. Great accuracy can be obtained with the system if all the necessary corrections (6) are taken into account; even without these corrections the system is a valuable adjunct to ventilatory care, especially in patients producing abnormal amounts of CO_2.

The above also answers Dr. Sladen's second question, namely what measures would improve ventilatory management in the early postoperative period. The difficulties he observes are in part due to CPB technique. The method in Lund is to follow rectal temperature during rewarming, and to cease CPB at 34°C. The perfusate temperature is 38°C, and thus central temperature will have been at 38°C for some time; the rectal temperature is the endpoint. Because of this more generous rewarming, the mean rectal temperature on arrival in the ICU is 35.8°C, one degree greater than in Dr. Sladen's study. It can be argued that this pro-

cedure increases perfusion time, but it is without doubt one way of reducing the patient's needs to generate extra heat by shivering, with subsequent undesirable effects such as increased oxygen consumption.

The early postoperative adaptation with peripheral vasoconstriction and metabolic changes seems to be caused by perioperative heat loss. In Uppsala this is combated by not only warming adequately before discontinuing CPB, but also in the ICU, by actively rewarming with the aid of a radiant heating ceiling suspended above the patient (7). This virtually eliminates postoperative shivering. Oxygen consumption and CO_2 production do not increase significantly above basal values (8), and thus setting the ventilator becomes a simpler task. The active warming is important in enabling safe early extubation as practised in Uppsala.

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References

1. Sladen RN. Temperature and ventilation after hypothermic cardiopulmonary bypass. Anesth Analg 1985;64:816–20.
2. Malmkvist G, Fletcher R, Jonson B, Jansson L. On-line deadspace measurement during cardiac surgery. Clin Physiol 1985;5(suppl)3:147–8.
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In Response:

The comments by Drs. Fletcher, Tydén, and Joachimsson are particularly welcome, since they confirm our subsequent work in this area and point to a possible means of preventing shivering after hypothermic cardiopulmonary bypass (CPB). In a study of 22 patients after hypothermic CPB (1), we found that although dead space to tidal volume ratio (V_D/V_T) was moderately increased on admission to the ICU (0.48 ± 0.6), it did not change significantly during rewarming over the next 8 hours. In the same study, we found that end-tidal CO_2 ($ETCO_2$) was very useful in tracking arterial PCO_2. The correlation coefficient between changes in $ETCO_2$ and changes in arterial PCO_2 was 0.94 ($P < 0.0001$).

In a related study (2), we demonstrated the importance of postoperative shivering in the genesis of metabolic in-

stability. After surgery there was a 50% increase in CO_2 production in patients who shivered, compared with only 19% in patients who did not shiver. Sixty percent of patients who shivered developed an acute respiratory acidosis on mechanical ventilation (arterial $PCO_2 > 50$ mm Hg, pH < 7.30); this did not occur at all in patients who did not shiver. These findings attest to the importance of preventing postoperative shivering in the reduction of metabolic instability.

Although I agree that the rectal temperature is a more meaningful indicator of total body warming of CPB than the esophageal or nasopharyngeal temperature, it has been my personal observation that attempts to improve this by prolonging perfusion time do not necessarily prevent postoperative shivering. Indeed, Drs. Joachimsson and Tydén appear to have confirmed this in their own work (3). We found that the use of heated, humidified gases alone after CPB did not significantly decrease the incidence or severity of postoperative shivering (4).

The use of postoperative radiant heating in Uppsala thus represents a very welcome possible solution to this frustrating problem. Presumably cutaneous warming suppresses shivering by altering the hypothalamic set point. However, since the correspondents' two abstracts (3,5) present no data, it would seem reasonable to examine their results in detail before accepting their conclusions.

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5. Tydén HE, Joachimsson PO, Nystrom SO. Ventilatory and metabolic effects of external heat supply after aortocoronary bypass surgery. Acta Anaesth Scan 1985;29(suppl 80):80.

Extending the Life of Oximetry Monitoring Probes

To the Editor:

We read with interest the technique for stabilization of oxygen monitor probes described by Samuels and Shochat in their Letter to the Editor (Anesth Analg 1986;65:213).

We have been utilizing a different approach for quite some time. Our method not only stabilizes the probe, but allows it to be used on multiple occasions.

Continuous measurement of oxygenation has virtually become a standard monitor in most operating rooms. At our institution, we use the Nellcor Pulse Oximeter. Both a

disposable and a nondisposable finger probe is available for use with the oximetric unit. We have occasionally found the nondisposable probe to be heavy and cumbersome. Our preference is to use the disposable probe because it is lighter, easier to apply, and less expensive. Also, this probe may be used on several patients prior to disposal.

Initially we found several drawbacks to this probe: 1) the adhesive strips tend to get dirty and stick to themselves and thus make application difficult if not impossible; 2) any solutions used around the probe may affect or destroy its performance; and 3) readjusting the probe after its application is usually difficult.

We have found a quick and easy method that not only obviates the above disadvantages, but significantly extends the useful life of the disposable probe. After carefully trimming off the adhesive tape that comes with the probe, it is applied to the nail bed in the usual fashion. A finger cot is then rolled over the finger, and the probe is held snugly in place. The probe is now protected from solutions, moisture, dirt, or dislodgment, and can be simply readjusted if necessary. The life expectancy of the probe may almost double, certainly a cost effective measure.

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Erroneous Blood Pressure Readings during and after IMA Dissection for CABG Surgery

To the Editor:

Kinzer et al. (1) reported on the erroneous arterial blood pressure reading during asymmetrical chest retraction necessary for internal mammary artery (IMA) dissection, despite proper functioning of all aspects of the monitoring system. They mentioned tension development at the juncture within the subclavian artery during retraction as the probable cause. The problem was solved by removal of the chest wall retractor.

A similar problem of erroneous blood pressure recording was observed in a patient during dissection of the IMA. Mechanical and electronic failure were also excluded. However, the problem continued after release of the unilateral sternal retractor: erroneous low arterial pressures were still observed during the use of a normal sternal retractor, thus during cardiopulmonary bypass, and also after discontinuation of perfusion. Accurate radial arterial pressure recordings were observed only after removal of the regular symmetrical chest retractor. Abnormal tracings could be reproduced easily by only limited spread of the sternum.

In this patient, compression of the subclavian artery occurred even with symmetrical sternal spread. Reviewing the literature, Saka et al. (2) described a similar problem, namely erroneous blood pressure recording even during symmetrical sternal spread, which was not mentioned by Kinzer et al. (1).

It has to be stressed that erroneous blood pressure readings from a radial artery catheter might occur not only during asymmetrical chest retraction, used during dissection of the IMA, but also with symmetrical sternal spread.

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References

1. Kinzer JB, Lichtenthal PR, Wade LD. Loss of radial artery pressure trace during internal mammary artery dissection for coronary artery bypass graft surgery. Anesth Analg 1985;64:1134–6.
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ERRATUM

The fact that Thrombelastograph® is a trade name inadvertently was not indicated in the article by Kang et al. (Anesth Analg 1985;64:888–96).

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Nicholas M. Greene, MD
Editor in Chief
Anesthesia and Analgesia
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   The Royal Marsden Hospital Bone-Marrow Transplantation Team. Failure of syngeneic bone-marrow graft without preconditioning in post-hepatitis marrow aplasia. Lancet 1977;2:242–4.

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   DuPont B. Bone marrow transplantation in severe combined immunodeficiency with an unrelated MLC compatible donor. In: White HJ, Smith R, eds. Proceedings of the third annual meeting of the International Society for Experimental Hematology. Houston: International Society for Experimental Hematology, 1974:44–6.

10. *Monograph in a Series*
    Hunninghake GW, Gadek JE, Szapiel SV, et al. The human alveolar macrophage. In: Harris CC, ed. Cultured human cells and tissues in biomedical research. New York: Academic Press, 1980:54–6. (Stoner GD, ed. Methods and perspectives in cell biology; vol. 1).

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    Ranofsky AL. Surgical operations in short-stay hospitals: United States—1975. Hyattsville, Maryland: National Center for Health Statistics, 1978; DHEW publication no. (PHS) 78–1785. (Vital and health statistics; series 13; no. 34).

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General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenic response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:

Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Adults: A Tracrium dose of 0.4 to 0.5 mg/kg (1.7-2.2 times the ED_{95}), given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. No Tracrium dosage adjustments are required for patients with renal disease.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended for adults following the use of succinylcholine for intubation under balanced anesthesia. Further reductions may be desirable with the use of potent inhalation anesthetics. The patient should be permitted to recover from the effects of succinylcholine prior to Tracrium administration. Insufficient data are available for recommendation of a specific initial Tracrium dose for administration following the use of succinylcholine in children and infants.

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a noteworthy advantage of enflurane anesthesia, particularly when epinephrine for hemostasis is required.

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mood and symptoms may persist for several days after administration.
Laboratory Tests: Bromsulfalein (BSP) retention occasionally is mildly increased post-operatively. This may be the result of surgery itself since anesthesia for 5 to 7 hours in volunteers does not increase BSP. Glucose and white blood count increase intra-operatively. Glucose elevation should be considered in diabetic patients.
Pregnancy Category B: Reproduction studies in rats and rabbits given four times the human dose of enflurane revealed no impairment of fertility or harm to the fetus. However, no adequate studies have been done in pregnant women, and enflurane should be used during pregnancy only if clearly needed.
Nursing Mothers: Enflurane may be excreted in human milk and caution should be exercised when enflurane is administered to a nursing mother.
Malignant Hyperthermia: In susceptible individuals, enflurane may trigger a hypermetabolic state and the clinical syndrome of malignant hyperthermia. The syndrome includes muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure (these nonspecific signs also may appear with light anesthesia, acute hypoxia, etc.). The increase in metabolism may elevate temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and increase the usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support, and management of electrolyte-fluid-acid-base derangement. Renal failure may appear and urine flow should be sustained if possible.

ADVERSE REACTIONS
1. Malignant hyperthermia (see PRECAUTIONS). 2. Deep levels of enflurane anesthesia and/or light levels with hypocapnia may produce convulsive activity. 3. Hypotension and respiratory depression may occur. 4. Arrhythmias, shivering, nausea, and vomiting have been reported. 5. Leukocytosis has been observed. 6. Unexplained mild, moderate, and severe liver injury may rarely follow anesthesia with enflurane.

OVERDOSAGE
To treat overdosage, stop drug administration, establish a clear airway, and assist or control ventilation with pure oxygen.

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REFERENCES: 1. Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Anal* 1974;53:361-364. **2.** Tornetta FJ: A comparison of droperidol, diazepam, and hydroxyzine hydrochloride as premedication. *Anesth Anal* 1977;56:496-500. **3.** Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Curr Ther Res* 1984;35:715-720.
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devoted to the publication of developmental studies

Editor-in-Chief

D. P. PURPURA, Brain Research, Office of the Dean, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, U.S.A.

Aims and Scope

Developmental Brain Research is a special section of *Brain Research* which provides a medium for prompt publication of in vitro and in vivo developmental studies concerned with the mechanism of neurogenesis, neuron migration, cell death, neuronal differentiation, synaptogenesis, myelination, the establishment of neuron-glia relations and the development of various brain-barrier mechanisms.

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PAVULON
(pancuronium bromide, injection)

BRIEF SUMMARY
[Please consult package insert for full prescribing information.]

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

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Anesthesia and Analgesia

Contents

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Over a decade of on-line antiemetic experience

Inapsine®
(droperidol) Injection

Significantly Superior Postoperative Antiemetic Prophylaxis

Please see next page for brief summary of Prescribing Information.

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INDICATIONS: INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction and as an adjunct in the maintenance of general and regional anesthesia; • in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE* (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.
Vital signs should be monitored routinely.

Usual Adult Dosage
I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.
II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
If INNOVAR* injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.
III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.
IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

How Supplied: *2 ml. and 5 ml. ampoules*—packages of 10; *10 ml. multiple-dose vials*—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
March 1980, Revised June 1980   IP41C98-M
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REFERENCES: 1. Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Anal* 1974;53:361-364. **2.** Tornetta FJ: A comparison of droperidol, diazepam, and hydroxyzine hydrochloride as premedication. *Anesth Anal* 1977;56:496-500. **3.** Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Curr Ther Res* 1984;35:715-720
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DEVELOPMENTAL BRAIN RESEARCH

A Section of Brain Research
devoted to the publication of developmental studies

Editor-in-Chief

D. P. PURPURA, Brain Research, Office of the Dean, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, U.S.A.

Aims and Scope

Developmental Brain Research is a special section of *Brain Research* which provides a medium for prompt publication of in vitro and in vivo developmental studies concerned with the mechanism of neurogenesis, neuron migration, cell death, neuronal differentiation, synaptogenesis, myelination, the establishment of neuron-glia relations and the development of various brain-barrier mechanisms.

Editorial Board

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A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]

Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery (Adapted from Hess et al[3]).

● ○ —·—·—·— Pretreatment (fentanyl, flunitrazepam, pancuronium)
● ——————— Treatment with isoflurane
○ — — — — — Treatment with halothane

Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

Post-laparoscopy Nausea (N) and Vomiting (V)		
Group	**No. of Patients**	**No. of Patients with N or N&V**
fentanyl, N_2O, O_2	37	23 (62%)*
isoflurane, fentanyl, O_2	20	6 (30%)
isoflurane, O_2	20	5 (25%)

Adapted from Alexander et al[8]   *$p<0.05$

References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981.   3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983.   4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971.   5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709.   6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981.   8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

For complete use information, please see following page.

Forane®...a product of original Anaquest research
(isoflurane)

Forane®...The Versatile Anesthetic
(isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION: FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:

$$F-\underset{\underset{F}{|}}{\overset{\overset{F}{|}}{C}}-\underset{\underset{Cl}{|}}{\overset{\overset{H}{|}}{C}}-O-\underset{\underset{F}{|}}{\overset{\overset{F}{|}}{C}}-H$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where:} \quad A = 8.056$$
$$B = -1664.58$$
$$T = °C + 273.16 \text{ (Kelvin)}$$

Partition coefficients at 37 °C

Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8

Partition coefficients at 25 °C - rubber and plastic

Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5

Purity by gas chromatography	>99.9%

Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY: FORANE (isoflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N₂O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO₂, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (5 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE: FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS: Known sensitivity to FORANE (isoflurane) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS: Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS: General: As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N₂O. See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (hot canister). PaO₂ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS: Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION: Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;

b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\% \text{ isoflurane} = \frac{100\, P_V\, F_V}{F_T\,(P_A - P_V)}$$

where:
P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED: FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0117

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- ☐ Carbon Dioxide
- ☐ Blood Pressures
- ☐ Temperatures

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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1986 Awards

The Board of Trustees of the IARS is pleased to advise that four Awards were granted and announced at the March 1986 meeting in Las Vegas, as follows:

Zeljko J. Bosnjak, PhD, Medical College of Wisconsin, Milwaukee, WI:
  "Effects of Chronic Administration of Calcium Antagonists"
John F. Butterworth IV, MD, Bowman Gray School of Medicine, Winston-Salem, NC:
  "Brain Cellular Mechanisms of Increased Anesthetic Susceptibility with Aging"
Philippe R. Housmans, MD, PhD, Mayo Foundation, Rochester, MN:
  "Influence of Halothane on Intracellular Calcium Handling in Mammalian Cardiac Muscle"
Vladimir Nigrovic, MD, Medical College of Ohio, Toledo, OH:
  "Adverse Reactions and Metabolism of Atracurium"

1987 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1987 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.

- The applicant must be a member of the International Anesthesia Research Society.

- Applications must be received in the IARS Cleveland office no later than December 15, 1986.

- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

> International Anesthesia Research Society
> 3645 Warrensville Center Rd.
> Cleveland, OH 44122
>   Telephone: (216) 295-1124

The 1987 Award(s) will be announced at the Annual Scientific Meeting (61st Congress) of the International Anesthesia Research Society to be held at the Buena Vista Palace, Lake Buena Vista (Orlando), Florida, March 14-18, 1987.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

IARS 61st CONGRESS TO BE HELD

March 14–18, 1987—BUENA VISTA PALACE, LAKE BUENA VISTA (ORLANDO), FLORIDA

CALL FOR PAPERS

August 13, 1986 DEADLINE

The Program Committee for the IARS 61st Congress would be pleased to receive abstracts for consideration as oral or poster presentations at the 1987 meeting in Florida. The official abstract application and transmittal forms are available from the Cleveland office of the IARS:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

Please note the absolute deadline for receipt of completed applications is August 13, 1986. To make certain you don't miss the August 13 deadline, please request forms promptly—either by calling the telephone number above, or returning the form below.

Noel W. Lawson, MD, Chairman
61st Congress Program Committee

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send _____ abstraction submission form(s) for the IARS 61st Congress to:
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     Address: _____
                _____

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Editorial

Halothane Hepatotoxicity—Again?

Another stimulating study from Tucson, Arizona! The article by Lind et al. (1) in this issue of *Anesthesia and Analgesia* is devoted to anesthesia-induced hepatotoxicity, an important and controversial issue in modern anesthesiology. The paper determines the oxygen concentration required for reductive metabolism of halothane by using hepatic microsomes obtained from rats pretreated with phenobarbital (PB) or polychlorinated biphenyl (PCB). The authors clearly demonstrate that reductive metabolism of halothane starts at 2% oxygen in control and at 5% in microsomes of rats pretreated with either PB or PCB. Compliments should be given to the investigators for having enough courage and confidence in their work to submit a paper describing a study on two rats per group, as well as to the editorial board and the editor-in-chief of *Anesthesia and Analgesia* for their ability to properly evaluate such a study.

The authors demonstrate that an increase in reductive metabolism of halothane is not proportional to the increase in cytochrome P-450 enzymes. Apparently both PB and PCB induce isoenzymes responsible for the reductive biotransformation of halothane (see reference 1, Table 1, first column), whereas PCB also enhances activity of other isoenzymes (see reference 1, Table 1, second column), thereby increasing oxygen demand to a greater extent than PB. The authors suggest that this increase in oxygen requirement results first, in a decrease in the oxygen supply–demand ratio, and second, in an increase in reductive metabolism of halothane due to more prominent tissue oxygen deprivation. It might be true. However, the second part of their speculations is not needed for the explanation of the data: a decrease in hepatic oxygen supply–demand ratio per se may be responsible for the observations.

What place does this study hold among other experimental data on anesthesia-induced hepatotoxicity? *The metabolic theory* of halothane-induced hepatotoxicity assumes that halothane undergoes a reductive biotransformation during hypoxic conditions that results in production of hepatotoxic intermediates. Opposing this is *the hypoxic theory* which suggests that hepatic damage is due to a decrease in the hepatic oxygen supply–demand ratio severe enough to cause hepatic necrosis without any significant role of halothane metabolism per se. The pertinent data are referenced, and pros and cons for either theory are presented in several comprehensive reviews (2–5). Several animal models have been developed to study anesthesia-induced hepatotoxicity: the hypoxic phenobarbital-pretreated rat, the nonhypoxic triiodothyronine (T_3)-pretreated rat, and the nonhypoxic, nonpretreated guinea pig.

Hypoxic Phenobarbital-Pretreated Rat

In 1972 it was described that halothane injected intraperitoneally in rats pretreated with phenobarbital could lead to liver necrosis (6). In the late 1970s, central lobular hepatic necrosis was demonstrated in rats pretreated with phenobarbital and anesthetized with halothane under hypoxic conditions (7–9). The reproducibility of liver damage depends on species, sex, age, temperature, and even season variations. The supporters of the metabolic theory believe that particular animals (and patients developing halothane-induced liver damage) possess an enhanced ability to biotransform halothane, thereby producing toxic reactive intermediates. However, supporters of the hypoxic theory may argue that these particular animals develop an unusually dramatic decrease in hepatic blood and oxygen supply under halothane and/or have a higher metabolic rate and therefore a higher hepatic oxygen demand than animals not developing liver injury under similar experimental conditions. This may lead to a substantial decrease in hepatic oxygen supply–demand ratio with subsequent liver injury without necessary involvement of halothane metabolism to reactive intermediates. A similar hypothesis could be developed from the knowledge that certain inhibitors of drug metabolism (SKF-525A, metyrapone, cimetidine) have a protective effect against halothane-induced hepatic injury in the rat model. These data

fit the metabolic hypothesis; however, these drugs decrease oxidative metabolism, thereby reducing hepatic oxygen requirement and improving the hepatic oxygen supply–demand relationship. Thus this group of data may fit both the metabolic and the hypoxic concepts of halothane hepatotoxicity.

Similar degrees of reductive metabolism of halothane may be accompanied by very different degrees of hepatic injury (10). The end products of reductive metabolism of halothane, namely fluoride; 2-chloro-1,1,1-trifluoroethane (CTF); and 2-chloro-1,1,-difluoroethylene (CDF), have never been found hepatotoxic. Different degrees of liver damage were described despite similar levels of CTF and CDF in the expired air. Moreover, liver damage could not be reproduced by exposure to CTF and CDF (3). Free radical intermediates have also been blamed for halothane-induced liver damage. However, the extent of free radical formation in the rat is not reflected in hepatotoxicity (3).

Enflurane, isoflurane, thiopental, and fentanyl can also produce liver damage. These data are difficult to explain from the metabolic theory standpoint since none of said drugs undergo reductive metabolism. However, these observations may result from hepatic oxygen deprivation per se while halothane may induce hepatic injury by different mechanisms. In a recent study, heated rats were exposed to enflurane and severe hypoxia, while hypothermic rats were treated with halothane and moderate hypoxia (11). It is not surprising that enflurane produced severe and early hypoxic damage while halothane combined with less severe hypoxia and lower body temperatures produced not necessarily metabolic, but rather slow and late hypoxic injury. However, halothane appears to be more destructive to the liver than other anesthetics. The difference can be explained by a more pronounced hepatic oxygen deprivation resulting not so much from respiratory as from circulatory depression during halothane compared to other anesthetics. It has been demonstrated in dogs, and in rats, that halothane disturbs hepatic circulation, thereby decreasing hepatic oxygen supply to a greater extent than either enflurane or isoflurane when used in equipotent doses according to MAC and degree of decrease in cardiac output and blood pressure (12–15). The inverse association between degrees of hepatic injury and values of hepatic oxygen supply, regardless of the insult that was used to vary hepatic oxygen supply (halothane, isoflurane, or hemorrhage), has been demonstrated (15). However, the direct association between a reduction in hepatic oxygen supply and the degree of injury does not prove the hypoxic

theory since, according to the metabolic theory, hepatic oxygen deprivation is a necessary condition for the reductive metabolism of halothane. Thus the data from this model have not proven the metabolic nor the hypoxic theory of anesthesia-induced hepatotoxicity.

Nonhypoxic Triiodothyronine

Triiodothyronine-pretreated rats exposed to halothane, enflurane, or isoflurane without hypoxia develop hepatic necrosis (16,17). Hyperthyroidism does increase overall the metabolic rate and also the metabolism of halothane and enflurane, but at the same time reduces cytochrome P-450 enzyme content in the liver, leading to a reduction in halothane metabolism. Triiodothyronine pretreatment also reduces cytochrome P-450 content and stimulates oxygen consumption. It appears that deterioration of the hepatic oxygen supply–demand relationship plays a decisive role in anesthesia-induced liver injury in this model (5).

Nonhypoxic, Nonpretreated Guinea Pigs

More than 10 years ago, it was reported that halothane induced liver damage in the guinea pig (18,19). Recently, hepatic necrosis has been observed in nonpretreated, nonhypoxic guinea pigs after halothane but not after isoflurane anesthesia (20). The authors observed that inorganic fluoride excretion was higher after halothane anesthesia in hypoxic conditions compared to normoxia, while the incidence and severity of hepatic injury was similar in each group treated with halothane, regardless of the difference in oxygen concentration provided. The authors attributed the observed hepatic necrosis to halothane biotransformation. However, the study confirms only that the reductive metabolism of halothane is enhanced during hypoxia in the guinea pig. The data actually suggest that halothane metabolism has little to do with halothane-induced liver damage. If hepatic damage were related to halothane metabolism, the severity of liver injury should have been associated with an increase in metabolites produced during the reductive biotransformation of halothane—it did not happen. The authors also speculate that hepatic oxygen supply during halothane and isoflurane anesthesia was similar because of similar changes in heart rate, blood pressure, and respiration, while liver damage was more pronounced after halothane than isoflurane anesthesia. However, there is enough data demonstrating that halothane and isoflurane given in equi-

potent doses according to MAC and according to a reduction in cardiac output and blood pressure are associated with very different degrees and patterns of hepatic circulatory disorders, resulting in a much better hepatic oxygen supply during isoflurane than during halothane anesthesia (12,13,15). Thus the rather limited available data with this model do not rule out the hypoxic theory of halothane-induced hepatotoxicity.

Indeed, it is extremely difficult to prove which of these two proposed mechanisms (metabolic vs hypoxic) is responsible for hepatic injury. Reductive biotransformation of halothane requires hepatic oxygen deprivation, while hepatic oxygen deprivation followed by restoration of hepatic blood flow may produce oxygen-derived free radicals (e.g., O_2^-, OH^-)by mechanisms dependent on accumulation of purine metabolites and transformation of xanthine dehydrogenase to free radicals producing xanthine oxidase during hypoxia (21). These oxygen-derived free radicals (with no relation to halothane) may cause liver damage indistinguishable from the damage produced by intermediates of reductive halothane biotransformation.

What place do the experimental models have in the whole spectrum of perioperative liver dysfunction in humans? Animal studies have been very exciting, but do not provide a clear understanding of the etiology and pathogenesis of halothane-induced hepatotoxicity in humans. Contrary to the clinical situation, there is some evidence of dose-related liver damage in the experimental model, especially in hypoxic rats. Multiple exposure to halothane does not play a significant role in the hepatic injury; it probably does the opposite—repeated exposure to halothane in the rat model may lead to a reduction in the incidence of liver necrosis. On the other hand, enzyme induction does not play a visible role in humans in anesthesia-induced hepatotoxicity. None of the identified metabolites have been shown to be hepatotoxic in humans. Also, an increase in the reductive biotransformation of halothane in patients who developed fulminant halothane hepatitis has not been clearly demonstrated.

Both old and recent data strongly suggest that fulminant halothane hepatitis is "allergic," "idiosyncratic," and immunologically mediated. Interestingly, halothane-mediated membrane antigenic changes (which are probably responsible for the hepatic damage) occur when the oxidative pathway of halothane biotransformation is activated (22). This observation does not fit the metabolic theory since, according to the metabolic hypothesis, the reductive (rather than oxidative) metabolism of halothane is required to produce liver injury.

The hypersensitivity hypothesis of halothane hepatitis does not exclude the metabolic and/or hypoxic theory of anesthesia-induced liver damage: hypoxia and/or halothane biotransformation may be responsible for the production of a hapten which is capable of provoking an immune response, resulting in severe hepatic necrosis. Obviously, fulminant halothane-hepatitis may have a completely different pathogenesis involving the immune system. Genetic predisposition to halothane-induced liver damage in animals, as well as in humans, may not imply the necessity of a genetically determined deviation in liver enzymes. It can be related to a genetically determined deviation in the immune system. Thus the mystery of anesthesia-induced hepatotoxicity has not been solved yet.

How should it influence our behavior in the operating room today? Common sense dictates that regardless of the precise mechanism of anesthesia-induced liver injury, hepatic oxygen deprivation must be avoided because it is required for liver injury according to both theories. Also, halothane must be used with extreme caution for the following reasons: 1) halothane is needed for formation of toxic intermediates if the metabolic theory is correct; 2) halothane decreases hepatic blood and oxygen supply more than other routinely used anesthetics, and hepatic oxygen deprivation is required for liver damage according to both theories; and 3) halothane induces fulminant hepatitis rarely but still more often than other anesthetics, if other anesthetics do at all. It does not appear to be difficult to decrease usage of halothane since other available anesthetics and techniques are capable of achieving almost everything that can be achieved with halothane.

Despite meteoric developments in concepts and technology in modern anesthesiology and intensive care, the postoperative mortality in patients with liver disease remains extremely high, averaging overall 31–67% and exceeding 90% in certain subgroups (23,24). There are many reasons for such high mortality as well as many forms of perioperative liver dysfunction and failure as listed below. Fatal fulminant halothane hepatitis is a rare clinical event, and does not appear to be directly linked to reductive biotransformation of halothane or hepatic oxygen deprivation. It is probably immunologically mediated and represents an entity completely different from other forms of perioperative liver injury.

It is important to realize that viral hepatitis can and apparently does develop in some patients during their perioperative period. Surgical stress and anesthesia may suppress immune responses, thereby aggravating chronic hepatitis and predisposing the carrier of the virus to an acute form of viral hepatitis. Viral

hepatitis may be very difficult to distinguish from true halothane-hepatitis and some other forms of liver damage. Infection or septicemia, incompatible blood transfusion, and drug-induced liver damage also may be responsible for perioperative liver injury.

This observer believes that the most common reason for liver damage occurring perioperatively in humans appears to be hepatic oxygen deprivation resulting from respiratory and mainly circulatory disorders. Surgical trauma and hemorrhage apparently play the main roles in perioperative liver circulatory disturbances (25). Anesthesia per se may further decrease hepatic blood and oxygen supply or, on the other hand, appropriate anesthesia management may protect the liver from surgical stress, relatively improving hepatic oxygenation (25). Cautious use of halothane and meticulous attention to respiratory and especially cardiovascular function to provide adequate oxygen delivery to the liver represent the best means of preventing hepatic complications.

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Oxygen Concentrations Required for Reductive Defluorination of Halothane by Rat Hepatic Microsomes

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LIND RC, GANDOLFI AJ, SIPES IG, BROWN BR Jr, WATERS SJ. Oxygen concentrations required for reductive defluorination of halothane by rat hepatic microsomes. Anesth Analg 1986;65:835-9.

The free oxygen concentrations required for reductive defluorination of halothane by rat hepatic microsomes from control and phenobarbital- (PB) and polychlorinated biphenyl- (PCB) treated animals were determined. Halothane-exposed microsomes from treated rats generated measurable levels of fluoride ion after 30 min incubations with oxygen concentrations of 5% or less. Microsomes from control animals produced fluoride only if the free oxygen concentration was 2% or less. During anoxic (0% oxygen) incubations, defluorination rates of 2.10 ± 0.17, 5.55 ± 0.38, and 5.46 ± 0.30 nmol fluoride·mg protein^{-1}·30 min^{-1} were observed for microsomes from control, PB, and PCB rats, respectively. Normalizing the maximal rates of defluorination to the microsomal cytochrome P-450 content yielded values of 5.14 ± 1.40, 3.70 ± 0.15, and 2.38 ± 0.26 nmol fluoride·nmol cytochrome P-450^{-1}·30 min^{-1} for control, PB, and PCB microsomes, respectively. Oxygen concentrations required for reductive metabolism of halothane by isolated rat hepatic microsomes are close to normal physiologic free oxygen concentrations of 4-5% reported for centrilobular areas of the rat liver. Thus even slight reductions in hepatic oxygenation during anesthetic exposure could lead to enhanced reductive biotransformation, an observation found in rat models of halothane-associated hepatic injury. The large differences among the treatment groups in the rates of fluoride ion generated per nanomole cytochrome P-450 indicate that enzyme induction regimens disproportionately increase those isozymes of hepatic cytochrome P-450 that are not involved with the reductive defluorination of halothane.

Key Words: ANESTHETICS, VOLATILE—halothane. LIVER—microsomes. METABOLISM—reductive.

Both oxidative and reductive pathways for the biotransformation of halothane are mediated by the hepatic cytochrome P-450 monooxygenase system (Fig. 1) (1–3). Oxidative biotransformation via insertion of activated oxygen is the preferred pathway, accounting for most of the total metabolism (4). However, when oxygen is in limited supply or is unable to interact with the cytochrome P-450, it is proposed that an electron is transferred to halothane, resulting in production of reactive intermediates and reductive defluorination of the molecule (5). This reductive metabolism has been associated with development of hepatic necrosis in animal models of halothane-induced hepatotoxicity (6,7), and has been reported to

occur in humans anesthetized with halothane (6). In rats, the induction of hepatic biotransformation enzymes by pretreatment with phenobarbital (PB) followed by exposure to the anesthetic in hypoxic (14% oxygen) atmospheres results in increased reductive metabolism of halothane and enhanced hepatic injury (6,8). With increases in rat hepatic enzyme levels induced by polychlorinated biphenyl (PCB), development of hepatic necrosis occurs even when exposures are carried out under hyperoxic (99% oxygen) conditions (9).

Thus, in animal models of halothane-induced hepatotoxicity, the inspired oxygen concentrations required for reductive biotransformation of halothane have, in part, been established. It is also known that isolated rat hepatocyte suspensions obtained from PB-treated rats reductively metabolize halothane even when incubated under atmospheres of 21% oxygen (10). Unfortunately, the single previous study that attempted to define the oxygen levels required for reductive halothane metabolism in isolated rat hepatic microsomes used only microsomes from PB-treated

Biotransformation of Halothane

$$
\begin{array}{c}
\hspace{3cm} \overset{O}{\underset{\parallel}{}} \\
\hspace{2cm} CF_3C\text{-}OH \ + \ Cl^- + \ Br^- \\
\hspace{1cm} O^{?} \diagup \\
CF_3CHClBr \diagup \ \ P\text{-}450 \\
HALOTHANE \diagdown \\
\hspace{1cm} e^{?} \diagdown \\
\hspace{2cm} [CF_3CHClBr]^- \!\!\longrightarrow\! CF_3CH_2Cl \ + \ CF_2CHCl \ + \ F^- \\
\hspace{2.5cm} \downarrow \\
\hspace{2cm} \text{Covalent Binding}
\end{array}
$$

Figure 1. Proposed pathways for the oxidative and reductive biotransformation of halothane by hepatic cytochrome P-450.

rats and reported a threefold variation in oxygen concentration values (11). Other studies comparing the effects of enzyme induction on the microsomal metabolism of halothane have been done only with 100% oxygen or 100% nitrogen atmospheres (1,5,12–15). Thus, the critical oxygen concentration for the occurrence of reductive metabolism of halothane at the membrane level and the effect of enzyme induction on this critical concentration are both still unknown. This study examines the free oxygen concentrations required for the reductive defluorination of halothane by hepatic microsomes isolated from control and PB- and PCB-treated male rats.

Materials and Methods

Animals

Male Sprague–Dawley rats (250–350 g) were obtained from the breeding colony at the Division of Animal Resources, University of Arizona (F_1 offspring of Hilltop Laboratories (Hilltop, PA) rats). They were housed in suspended steel cages at 22°C, kept on a 12 hr day/night cycle, and allowed food and water ad lib.

Chemicals

Sodium phenobarbital was obtained from the Mallincrodt Chemical Company (St. Louis, MO), Arochlor 1254 (PCB) from Monsanto Chemical Co (St. Louis, MO), and Fluothane (halothane) from Ayerst Laboratories (New York, NY). Glucose-6-phosphate, nicotinamide adenine dinucleotide phosphate (NADP), and glucose-6-phosphate dehydrogenase were all purchased from Sigma Chemical Company (St. Louis, MO). Nitrogen and oxygen gas cylinders were supplied by Liquid Air Corporation (San Francisco, CA). The total ionic strength activity buffer (TISAB) and stock 0.1M fluoride solution used in the fluoride analysis were purchased from Orion Research Incorporated (Cambridge, MA). All other chemicals and reagents utilized were of standard reagent grade.

Hepatic Microsomal Enzyme Induction Protocol
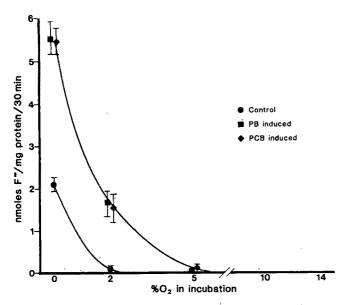
Phenobarbital-pretreated animals ($n = 2$) were given a single intraperitoneal injection of 100 mg/kg PB followed by 5 days of drinking water with 1 mg/ml PB. Fresh water was substituted for a 24-hr period before the animals were killed on day 6. Pretreatment of two rats with PCB consisted of four daily oral intubations of 100 mg/kg PCB in corn oil (50 mg PCB /ml) with the animals being killed on day 5. Control animals ($n = 2$) received four daily oral doses of corn oil (2 ml/kg) and were killed on day 5.

Hepatic Microsomal Isolation

Separate sets of microsomes were obtained from two animals in each treatment group. Animals were killed by cervical dislocation and their livers were quickly perfused via the portal vein with cold 0.05M Tris-HCl, 1.15% KCl, pH 7.4. The livers were weighed, minced, and subsequently homogenized in 3:1 (v/w) cold Tris buffer in a Dounce homogenizer. The homogenates were centrifuged at 4°C at 3000, 12,000, and 27,000 xg for 10 min each. The supernatant fractions were then centrifuged at 220,000 xg for 45 min to obtain a microsomal pellet that was resuspended in cold Tris buffer and stored at −80°C. Prior to use in the incubations, concentrations of microsomal protein (16) and cytochrome P-450 (17) were determined. Control microsomes contained a mean level of 0.43 nmol cytochrome P-450/mg protein, whereas enzyme induction with PB or PCB produced mean values of 1.50 nmol and 2.30 nmol, respectively.

Microsomal Incubations

Incubations with each set of microsomes were carried out in triplicate at each data point. Microsomes (12 mg in 4 ml Tris buffer) were placed in 25 ml Erlenmeyer flasks which were sealed with rubber septa. Background (nonenzymatic) levels of fluoride ion were determined by placing flasks containing microsomes in boiling water for 10 min before further treatment. By means of two 18-gauge needles inserted through the septa, flasks were flushed with nitrogen and oxygen mixtures containing 14, 10, 5, 2, or 0% oxygen. One needle allowed infusion of the gas mixture while the other served as a vent. The gas mixtures were delivered for 10 min at a flow rate of 250 ml·min^{-1}· flask^{-1} into as many as eight flasks at a time by a fluidic gas metering system designed and constructed by the Advanced Biotechnology Engineering Section (Department of Anesthesiology, University of Ari-

Figure 2. Oxygen concentration requirements for the reductive defluorination of halothane by isolated rat hepatic microsomes. Values are X ± SD of six determinations obtained from two animals (three per animal) in each treatment group.

Table 1. Effect of Cytochrome P-450 Induction on the Maximal Rates of Defluorination of Halothane by Rat Hepatic Microsomes In Vitro

Animal pretreatment	Fluoride generated over 30 min (nmol)	
	Per mg protein	Per nmol cytochrome P-450
Control	2.10 ± 0.17	5.14 ± 1.40
PB[a]	5.55 ± 0.38	3.70 ± 0.15
PCB[b]	5.46 ± 0.30	2.38 ± 0.26

Values are x̄ ± SD of six determinations obtained from two animals (three per animal) in each treatment group. Values expressed minus background fluoride levels of 0.33 ± 0.05 nmol fluoride•mg protein^{-1}•30 min^{-1}.

Abbreviations: PB, sodium phenobarbital; PCB, polychlorinated biphenyl.

[a]Treated with a single intraperitoneal injection of 100 mg/kg followed by five days of drinking water containing 1 mg/ml.

[b]Treated with four daily oral intubations of 100 mg/kg in corn oil.

zona). The flasks were swirled vigorously three times during the 10-min gassing period to help ensure equilibration of the microsomal suspension with the atmosphere. Fifty microliters of NADPH cofactor generating system containing 13 mM NADP, 170 mM glucose-6-phosphate, 20 U/ml of glucose-6-phosphate dehydrogenase, and 10 mM MgCl$_2$ were injected into each flask. The reaction was started by the addition of 2 µl of halothane into the suspension. Incubations were carried out at 37°C for 5–30 min in a Dubnoff Metabolic Shaking Incubator (GCA/Precision Scientific, Chicago, IL). Throughout the incubation period the microsomal suspensions were shaken vigorously to ensure constant mixing of the suspension with the particular atmosphere. The reaction was stopped by mixing 1 ml of microsomal suspension with 1 ml cold TISAB buffer (pH 5.0) which also allowed for subsequent fluoride analysis. To ensure that the substrate and cofactor were at saturation, incubations were also conducted with twice the quantity of halothane and NADPH generating system.

Fluoride Ion Analysis

The microsome–TISAB mixtures were analyzed for fluoride ion content by means of Orion specific ion electrodes. Standards were produced by serial dilution of a 0.1M fluoride stock solution. Care was taken to measure samples and standards from lowest to highest fluoride ion concentrations to avoid ion saturation effects on the selective ion electrodes.

Results

The defluorination of halothane by hepatic microsomes from control rats did not occur to a measurable extent until free oxygen tensions of 2% were used, with an abrupt increase to maximal rates at 0% oxygen (Fig. 2). On the other hand, hepatic microsomes from PB- and PCB-treated rats defluorinated halothane at identical rates, producing fluoride ion under free oxygen tensions as high as 5% oxygen. Again a steep curve was produced, with defluorination rates more than twofold greater than control values at 0% oxygen (Fig. 2, Table 1). Reaction conditions were optimal, as evidenced by the fact that doubling the amount of NADPH cofactor generating system or of substrate in the incubations led to no further generation of fluoride ion (data not shown).

The time course of fluoride evolution from PB- and PCB-induced microsomes in the absence of oxygen (0% oxygen) demonstrated that both groups metabolized halothane at the same rate over the 30 min incubation period (data not shown). When defluorination rates at 0% oxygen were normalized to the amount of cytochrome P-450 present, all three groups were quite different from each other, with microsomes from control rats producing more fluoride per nmole cytochrome P-450 than microsomes from either PB- or PCB-treated rats (Table 1).

Unfortunately, an n value of only two animals for each treatment group prevents statistical analysis of the data based on biological variability. With the high degree of precision demonstrated by the low standard deviations among the six determinations (three from each animal) at each data point, we expect that little difference in the data would be observed if a greater number of animals were used.

Discussion

Low concentrations of free oxygen (2–5%) were required for rat hepatic microsomes to reductively defluorinate halothane in vitro. Measurable fluoride generation occurred in microsomes from control rats only when the oxygen concentrations was 2% or less as compared with 5% oxygen for microsomes from PB- and PCB-induced animals (Fig. 2). These free oxygen concentrations required for the microsomal reductive defluorination of halothane lie near the range of values previously reported for phenobarbital-induced rat hepatic microsomes (11). The reported values of 20–60 μmol oxygen in solution with a mean of 34 μmol are equivalent to approximately 3–9% and 5% free oxygen, respectively (11,18). Furthermore the required oxygen concentrations are not dissimilar from reported in vivo levels of 4–5% free oxygen in the hepatic vein of the rat (18). Thus any decrease in hepatic oxygenation during in vivo exposure to halothane, whether caused by inspiration of a mildly hypoxic atmosphere as in the halothane–hypoxia rat model (4,6,8,15), or by decreases in liver blood flow induced by the anesthetic (19), would create a hepatic centrilobular environment conducive to reductive metabolism of halothane. Humans and guinea pigs have been shown to exhale volatile reductive halothane metabolites when anesthetized with halothane, even when inspiring high concentrations of oxygen (6,7). This finding implies that oxygen tensions in the centrilobular regions of their livers remain at low levels during halothane anesthesia regardless of inspired oxygen levels.

Although enzyme induction led to greater levels of reductive metabolism in isolated microsomes, the increase was not proportionate to increases in cytochrome P-450 enzymes, which indicates that the induction regimes increased a number of isozymes of cytochrome P-450 besides those involved in reductive dehalogenation of halothane (20). The identical rates of defluorination at 0% oxygen obtained for microsomes from PB and PCB-induced rats imply that both inducers equally enhanced isozymes responsible for the reductive biotransformation of halothane.

Induction of drug-metabolizing enzymes in vivo with PB or PCB increases both the size of centrilobular hepatocytes and the quantities of smooth endoplasmic reticulum and associated cytochrome P-450 contained within them (21–23). Although no oxygen gradient exists between the cell membrane and endoplasmic reticulum of enzyme-induced hepatocytes (24), a greater rate of oxygen consumption within the endoplasmic reticulum because of increased rates of oxidative biotransformation may produce a localized

intracellular hypoxia/anoxia. A lack of oxygen in the vicinity of the endoplasmic reticulum would thus enhance reductive metabolism. Pretreatment by PCl causes induction of cytochromes of the P-448 class a well as the cytochrome P-450 isozymes typically induced by PB (23). The subsequent level of oxidative metabolic flux in the endoplasmic reticulum of the hepatocytes of a PCB-treated rat may be so great a: to exceed the diffusion of oxygen into the cell ever when the animal is well-oxygenated during halothane anesthesia. This condition would then lead to the reductive metabolism and hepatotoxicity reported to occur under normal to high oxygen tensions in PCB pretreatment models of halothane-associated hepatotoxicity (9,25,26,).

In isolated rat hepatocyte suspensions, the reductive biotransformation of halothane occurs even when incubations are carried out under free oxygen concentrations several times greater than those occurring in vivo (10). This may well be a consequence of physical limitations of the incubation system. Isolated hepatocytes are kept suspended in the incubation medium by gentle swirling in order to prevent physical damage to the cells (10). Thus insufficient mixing of the media with the particular incubation atmosphere may well produce inadequate oxygenation of the hepatocytes. In order to minimize this potential problem in our study, a large surface area to volume ratio (4 ml of microsomal suspension in 25 ml Erlenmeyer flasks) was combined with vigorous shaking during the incubation period.

In summary, although it appears that very low free oxygen concentrations are required for rat hepatic microsomes to reductively biotransform halothane, these values are not dissimilar from the oxygen concentrations in the centrilobular regions of the liver. Thus even slight decreases in available oxygen, whether caused by reductions in inspired oxygen, diminished blood flow to the liver, or increased intracellular oxygen consumption as a result of enzyme induction would create an environment conducive to reductive halothane metabolism.

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Effects of Cimetidine and Ranitidine on Local Anesthetic Central Nervous System Toxicity in Mice

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KIM KC, TASCH MD. Effects of cimetidine and ranitidine on local anesthetic central nervous system toxicity in mice. Anesth Analg 1986;65:840–2.

The effects of cimetidine (5–200 mg/kg), ranitidine (1–100 mg/kg), or saline on local anesthetic central nervous system toxicity was studied when administered 20 min before the administration of lidocaine (30–80 mg/kg) or 2-chloroprocaine (50–250 mg/kg) to female white CD-1 mice. All drugs were administered intraperitoneally. The 50% convulsive dose (CD_{50}) was determined for each drug and dose combination. Pretreatment with cimetidine resulted in a significant, dose-dependent decrease in the CD_{50} of lidocaine, whereas ranitidine pretreatment did not significantly alter the lidocaine CD_{50}. A dose of cimetidine (15 mg/kg) that caused a significant decrease in 2-choloroprocaine CD_{50} (from 180 to 110 mg/kg) caused only an insignificant decrease in lidocaine CD_{50} (from 59 to 54 mg/kg). If these results can be applied to clinical doses in humans, ranitidine may be a safer premedicant than cimetidine with regard to interactions with local anesthetics.

Key Words: ANESTHETICS, LOCAL—toxicity. GASTROINTESTINAL TRACT, STOMACH—cimetidine, ranitidine.

With the increasing popularity of chronic and acute administration of cimetidine has come increasing awareness of the drug's interactions with other medications. Cimetidine may reduce hepatic blood flow and does inhibit some hepatic microsomal enzymes (1). Through one or both of these mechanisms, cimetidine reportedly impedes the metabolism of lidocaine, diazepam, propranolol, and a host of other drugs. Resulting toxic interactions have been described (2,3,4). The more recently introduced H-2 receptor antagonist, ranitidine, is reputed to leave drug metabolism unimpaired, and may thus be unlikely to contribute to toxic drug interactions (2). Both of these H-2 histamine receptor blockers are commonly used preoperatively to reduce gastric acidity and to lower the risk of pulmonary acid aspiration. We wished to determine whether these medications increase the risk of local anesthetic toxicity in the central nervous system.

Materials and Methods

The animals used in this study were female white mice of the CD-1 strain, weighing 20 ± 1 g, which were allowed free access to both food and water until the time of the experiment. All drugs were administered intraperitoneally in a volume of 0.005 ml/g body weight. Cimetidine, in doses ranging from 5 to 200 mg/kg, ranitidine, in doses from 1 to 100 mg/kg, or saline was injected intraperitoneally before the intraperitoneal injection of a local anesthetic. The anesthetics studied were lidocaine, in doses from 30 to 80 mg/kg, and 2-chloroprocaine, in doses from 50 to 250 mg/kg. The criteria used to define convulsion were loss of righting reflex, clonic and tonic seizure activity, and opisthotonus. Latency time (from anesthetic injection to the first clonic seizure), duration of seizure, and recovery time (to regaining normal gait after the seizure) were recorded.

To determine the mean 50% convulsive dose (CD_{50}), groups of ten mice were tested with various doses of the drugs until at least four points were established between doses at which 0% of mice and 100% of mice convulsed. Each of the 450 mice tested was used only once. The CD_{50} was computed from the probit-log dose regression line using the method of Litchfield and Wilcox (5). Parallelism and statistical significance were tested by the same method.

Results

The data in Table 1 indicate that, as the dosage of cimetidine increased, the CD_{50} of lidocaine decreased significantly in a dose-dependent fashion. On the other

Table 1. CD_{50} of Lidocaine after Cimetidine or Ranitidine

	Lidocaine CD_{50} (mg/kg)[a]	% of control CD_{50}
Cimetidine dose (mg/kg)		
0 Control	58 (54.6–63.7)	100
15	53 (48.2–61.0)	91
50	45 (40.7–52.2)	78[b]
100	40 (37.7–48.1)	69[b]
200	38 (31.4–44.5)	66[b]
Ranitidine dose (mg/kg)		
0 Control	65 (60.2–71.1)	100
7.5	58 (52.1–64.4)	89
25	56 (51.1–63.3)	86
50	58 (53.5–67.2)	89
100	58 (51.1–65.5)	89

[a]Range of 95% confidence limits in parentheses.
[b]Values significantly different from control.

hand, pretreatment with ranitidine resulted in only insignificant decreases in the CD_{50} of lidocaine at any dose. As shown in Table 2, a dose of cimetidine (15 mg/kg) that caused only an insignificant (9%) decrease in the CD_{50} of lidocaine resulted in a significant (39%) decrease in the CD_{50} of 2-chloroprocaine. An equivalent dosage of ranitidine (7.5 mg/kg) resulted in only insignificant decreases in the CD_{50} of both lidocaine and 2-chloroprocaine.

Latency time and duration of convulsion were similar in control and in cimetidine- and ranitidine-treated mice. Recovery time, however, varied among groups: the recovery time after seizure produced by lidocaine, 70 mg/kg, was 89% longer in the cimetidine group than in the ranitidine and control groups. Recovery times in control and cimetidine-treated mice were 7.3 ± 1.4 min and 13.8 ± 2.6 min, respectively.

Discussion

The liver metabolizes 70% of the lidocaine hematogenously delivered to it (4). This high hepatic extraction ratio means that lidocaine clearance is largely dependent on hepatic blood flow (HBF). Metabolism of lidocaine within the liver is accomplished by hepatic microsomal monooxygenase enzymes. Thus the systemic clearance of this amide local anesthetic is vulnerable to any agent that reduces HBF or interferes with hepatic microsomal enzymes. Cimetidine has been implicated in both areas; ranitidine, generally, has not. An agent that reduces lidocaine clearance would increase blood and tissue concentrations of lidocaine and enhance its potential toxicity.

The effect of H-2 receptor antagonists on HBF has been a controversial subject. Cimetidine has acquired a reputation for reducing hepatic perfusion, and one

study reported that HBF decreased 24% after acute cimetidine administration and 33% after repeated injections (1). Other studies, however, indicate that cimetidine does not affect HBF, systemic hemodynamics, or the proportion of cardiac output delivered to the liver (6,7). Similar controversy surrounds ranitidine. One study showed that hepatic clearance of indocyanine green (ICG), assumed to indicate HBF, decreased 19% after ranitidine administration (8). Another study demonstrated a 22% decline in ICG clearance after ranitidine, but no change in the gradient between free and wedged hepatic venous pressure. The authors considered this pressure gradient indicative of HBF, and thus interpreted their results to indicate a decrease in hepatic extraction ratio of ICG, but no decrease in HBF, after ranitidine (9). Therefore it cannot be said whether the different effects of the two H-2 antagonists on lidocaine CD_{50} are related to different effects on HBF.

There is greater agreement on the effects of cimetidine and ranitidine on hepatic microsomal enzyme activity. Cimetidine contains an imidazole ring, and several imidazole compounds have been found to inhibit hepatic monooxygenase activity (2). Cimetidine specifically has been shown to interfere with this enzyme system, perhaps by binding directly to cytochrome P-450. Interestingly, cimetidine does not inhibit hepatic glucuronidation. Glucuronyl transferase enzymes are buried more deeply in the endoplasmic reticulum than are oxidative enzymes, and it has been suggested that the former are thus more protected from cimetidine's access and influence than the latter (3). Ranitidine, on the other hand, does not contain an imidazole ring, and does not seem to interfere with hepatic oxidative enzymes. Cimetidine, but not ranitidine, has been found to reduce the metabolism of antipyrine and aminopyrine; this test is considered to reflect the activity of hepatic microsomal oxidative enzymes (2). Cimetidine, but not ranitidine, impairs the systemic clearance of lidocaine (4,10,11). This may reflect different effects of the two drugs on microsomal enzymes, and would be sufficient to explain our finding that cimetidine, but not ranitidine, significantly enhances the CNS toxicity of lidocaine. No effect of H-2 antagonists on HBF need be invoked.

Our findings may, however, be unrelated either to hepatic perfusion or to enzyme inhibition. Any factor that decreases the volume of distribution of lidocaine would increase the concentration of lidocaine in blood and in well-perfused tissues (such as brain) after any given dose. Increased risk of toxicity would ensue. Cimetidine reduces the steady-state volume of distribution of lidocaine by 20%. This could represent the simple displacement of lidocaine by cimetidine

Table 2. CD_{50} of Lidocaine and Chloroprocaine after Cimetidine or Ranitidine

	Anesthetic	Anesthetic CD_{50} $(mg/kg)^a$		% of control CD_{50}
Cimetidine dose (mg/kg)				
Control	Lidocaine	59	(52.2–66.7)	100
15	Lidocaine	54	(48.6–61.7)	91
Control	Chloroprocaine	180	(174.3–196.2)	100
15	Chloroprocaine	110	(100.9–122.7)	61^b
Ranitidine dose (mg/kg)				
Control	Lidocaine	59	(53.7–62.6)	100
7.5	Lidocaine	56	(48.6–61.7)	95
Control	Chloroprocaine	180	(174.3–196.2)	100
7.5	Chloroprocaine	162	(151.2–179.6)	90

^{a}Range of 95% confidence limits in parentheses.
^{b}Values significantly different from control.

from tissue binding sites (11). Ranitidine does not influence the volume of distribution of lidocaine (10). In our study, a dose of cimetidine that caused only a 9% decrease in the CD_{50} of lidocaine resulted in a 39% decrease in the CD_{50} of 2-chloroprocaine. 2-Chloroprocaine is metabolized by hepatic and plasma esterases, not the hepatic microsomal monooxygenase system. The fact that cimetidine had so much more profound an effect on the CD_{50} of 2-chloroprocaine than on the CD_{50} of lidocaine indicates that hepatic oxidative enzyme inhibition may not be the decisive factor in our findings. To our knowledge, the effects of cimetidine on the volume of distribution of 2-chloroprocaine and on the activity of plasma cholinesterase have not been established.

In conclusion, we found that cimetidine reduced the CD_{50} of lidocaine in mice in a significant and dose-related manner, whereas ranitidine did not. In addition, cimetidine caused a more profound reduction in the CD_{50} of 2-chloroprocaine than in that of lidocaine, and again, ranitidine did not. The possible contributions of reductions in hepatic perfusion, hepatic microsomal enzyme activity, and local anesthetic volume of distribution are discussed. While the indiscriminate use of H-2 receptor blockers is certainly subject to question, our study indicates that ranitidine may be a safer component of premedication than cimetidine when adverse drug interactions, specifically with local anesthetics, are considered. In attempting to apply our findings to the clinical situation, the ob-

vious limitations imposed by differences in species and in dosage must be recognized.

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Somatosensory Evoked Potential Quantification of Ulnar Nerve Blockade

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BENZON HT, TOLEIKIS JR, SHANKS C, RAMSEUR A, SLOAN T. Somatosensory evoked potential quantification of ulnar nerve blockade. Anesth Analg 1986;65:843–8.

We investigated the appropriateness of the somatosensory evoked potentials (SSEPs) as an objective monitor of sensory blockade of the ulnar nerve by comparing the effects of saline and lidocaine infiltration of the ulnar nerve at the elbow, with and without epinephrine. The four treatments were administered in random order to each of eight volunteers who were asked to assess the intensity of sensory blockade on a 10-cm visual analogue scale (SVAS). Concomitantly, ulnar nerve SSEPs were recorded at the Erb's point, over the posterior spine at or rostral to C-7, and over the sensory cortex. All 16 of the saline and saline with epinephrine infiltrations resulted in SVAS scores of 1 or less. In contrast, all the lidocaine and lidocaine with epinephrine injections were associated with SVAS scores in excess of 8. With lidocaine this lasted 83 ± 22 min, and the duration of lidocaine with epinephrine was 248 ± 82 min. SSEP responses were considered abnormal when there were 15 min or more of a decrease in amplitude by 50% or more and an increase in latency by 15% or more. After plain lidocaine injection, all the amplitude measurements showed depression over 50%, with the exception of cortical measurements in one subject. Similarly, there were increased latencies at Erb's point and C-7 with lidocaine blocks. In contrast, change in cortical latency was seldom seen. Variable selection by multiple linear regression analysis of the six SSEP measurements gave a statistical model that sensory block duration (SVAS ≥8) could be specified by the duration of the reduced C-7 amplitude ($r = 0.96$). We conclude that ulnar nerve SSEP monitoring provides an objective assessment of sensory blockade of the ulnar nerve.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—ulnar nerve block. MEASUREMENT TECHNIQUES—sensory blockade. MONITORING—evoked potentials.

Ulnar nerve block is commonly used to compare the characteristics, i.e., onset and duration, of nerve blockade produced by different local anesthetics (1–3). Motor blockade has been subjectively evaluated by assessment of the strength and motility of the fifth finger (1–3); it has been objectively evaluated by the electromyogram (3). Sensory blockade has been subjectively evaluated by pin-prick or pinch test (1–3). There has been no published objective evaluation of sensory blockade of a peripheral nerve. Somatosensory evoked potential (SSEP) monitoring has been used to examine the neurologic status of the unanesthetized brachial plexus (4,5). It therefore seemed appropriate to use the SSEP to objectively study the characteristics of sensory blockade of an ulnar nerve block.

This study compared the effect of saline and lidocaine infiltration of the ulnar nerve proximal to the elbow, with and without epinephrine, on the following: 1) the sensory visual analogue scale (SVAS) in response to pinching the fifth finger and hypothenar eminence, 2) motor visual analogue scale (MVAS) assessment of the motility and strength of the fifth finger, and 3) SSEPs recorded at the Erb's point, over the posterior spine at or rostral to C-7, and over the sensory cortex. The effect of epinephrine injection was studied because recent reports have raised the possibility of a local anesthetic effect of epinephrine (6–8). The study assessed the site at which SSEP measurements best correlate with subjective evaluation of somatic sensory function.

Methods

Eight healthy volunteers, 6 men and 2 women, 28–38 yr old were studied. All volunteers were anesthesiologists. Each volunteer had four ulnar nerve blocks with 5 ml of the following drugs: 1) preservative-free physiologic saline solution (PFPS), 2) PFPS with 1:200,000 epinephrine, 3) 1.5% lidocaine, 4) 1.5% lidocaine with 1:200,000 epinephrine. The epinephrine used was the commercially available preparation (Adrenaline®, Parke-Davis). The interval between injections was 1–2 weeks. If tenderness and discomfort at the site of injection and paresthesia to the fifth finger persisted after the injection, subsequent testing was not done until at least 1 week had elapsed from the time these symptoms disappeared. The sequence of injection was randomized with a Latin square design (9). The study was approved by the Human Subjects Committee of Northwestern University and the Research Committee of Northwestern Memorial Hospital. Written informed consent was obtained from all the volunteers.

Baseline tests done before the ulnar nerve block included testing of sensation of the fifth finger and hypothenar area; assessment of the strength and motility of the fifth finger; SSEP monitoring and recording of potentials at the ipsilateral Erb's point, over the posterior aspect of the spine at or slightly rostral to C-7, and over the sensory cortex; and, recording of the temperature of the fifth finger with a Yellow Springs Thermometer model number 427. Sensation was determined by pinching the fifth finger and the hypothenar area with a surgical clamp. After each pinch, the volunteers noted the presence or absence of numbness. If present, the degree of numbness was graded with an SVAS. The SVAS was a 10-cm line. The beginning of the line (zero cm end) stated "My little finger and hypothenar areas are not numb at all"; the terminal end (10 cm end) stated "My little finger and hypothenar areas are completely numb." The strength and motility (flexion, abduction, and adduction against resistance) of the fifth finger was determined by an MVAS. The MVAS was a 10-cm line. The 0 cm end stated "My little finger is very strong"; the 10 cm end stated "My little finger is very weak."

A multichannel signal averager (Nicolet Pathfinder II, Nicolet Biomedical, Madison, WI) was used to measure and record SSEPs. The SSEP recordings were done with the elbow partially extended at approximately 130°. This position was observed and maintained during each recording period. A pair of surface electrodes were placed over the ulnar nerve at the wrist, and stimuli were applied at a rate of 8.7 Hz at an intensity level slightly above motor threshold. Recording electrodes were placed at the ipsilateral Erb's point, dorsally at or rostral to C-7, and on the contralateral scalp over the neuronal generator areas (EEG International Ten Twenty locations C3' or C4'). The frequency bandpass for recording was 5–1000 Hz, and the sampling window was 50 msec. All electrode impedances were maintained at less than 2 kohms. Three groups of 250 averaged responses were acquired during each testing period. The responses were compared for reproducibility to demonstrate actual neurologic effects and to rule out false findings. Composites were formed from the three averages (total of 750 responses) from each recording site to improve the signal-to-noise ratio. Peak-to-peak amplitudes and latencies of the composite responses from all three recording sites were monitored and recorded. This technique is considered to be a standard technique for making differential diagnosis of a sensory pathway lesion (10). SSEP baseline measurements were repeated until values could be reduplicated immediately prior to each ulnar nerve infiltration.
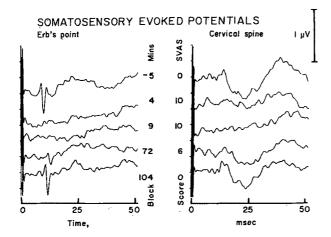
During performance of the ulnar nerve infiltration, the subject's arm was abducted and the elbow bent. The ulnar groove was located and a modified ulnar-nerve block performed (3). After aseptic preparation of the skin, a 25-gauge needle was inserted slightly proximally to the groove, approximately 1 cm proximal to the medial epicondyle, and advanced until paresthesia to the fifth finger was elicited. The needle was slightly withdrawn to prevent intraneural injection, and 5 ml of the drug was injected. The study was double-blind; the volunteers and the investigator (J.R.T.) who recorded, stored, and later measured the latencies and amplitudes of the different evoked potentials were not aware which solution was used during each injection.

After each injection, testing of the presence of sensory and motor blockade, SSEP testing, and recording of the skin temperature of the fifth finger were done at 2–5 min intervals up to 30 min, then every 15 min until sensory recovery. If there was no sensory blockade on the SVAS at 30 min, testing continued for an additional half hour. During regression of the nerve block, with each SVAS testing, each subject was asked when surgery on his or her fifth finger or hypothenar area would not be permitted anymore.

An SVAS score of 1 or less was considered a "no block"; a score of 8 or more was considered a "good block." This number was chosen because the volunteers stated, during recovery of their local anesthetic blockade, that surgery would not be permitted on their fifth finger and hypothenar area when the SVAS score was below 8. The duration of good block

SOMATOSENSORY EVOKED POTENTIALS

Figure 1. SSEP tracings of the Erb's point and C7 potentials with establishment and recovery from ulnar nerve blockade.

Table 1. Number of Volunteers with Significant Changes in SSEP Amplitude and Latency Lasting 15 Minutes or More

	A[a]	B	C	D
≥ 50% Decrease in amplitude				
Erbs	1	0	8	8
C7	0	0	8	8
Cortex	1	0	7	8
≥ 15% Prolongation of latency				
Erbs	0	0	8	8
C7	0	0	6	8
Cortex	0	0	1	1

A, saline; B, saline with epinephrine; C, 1.5% lidocaine; D, 1.5% lidocaine with epinephrine.
[a]Changes occurred in one subject.

was considered to be an index of useful local anesthetic effect.

The SSEP was considered to be abnormal when the following changes occurred for 15 min or more: a) decrease in amplitude by 50% or more (11), b) increase in latency by 15% or more. The duration of each SSEP abnormality was noted for each injection. With duration of the SVAS score of 8 or greater as the dependent variable, multiple linear regression (MLR) analysis was used to select which of the six SSEP values (≥50% decrease in amplitude and ≥15% increase in latency at the Erb's point, C-7, and cortex, respectively) adequately predicted the variable.

Results

Using the SVAS scores, we found that all the saline and saline with epinephrine injections resulted in no blocks, whereas all the lidocaine and lidocaine with epinephrine injections resulted in good blocks. The same results were obtained with the MVAS scores, with the exception of the lidocaine injection; one of the eight volunteers graded the maximal motor blockade of his fifth finger to be a 7.

During regression of the nerve blockade with lidocaine and lidocaine with epinephrine, the range of SVAS scores at which time surgery would no longer be permitted went from 5 to less than 8. The "duration of good block" (SVAS scores of 8 or greater) was 83 ± 22 min (range 42–105) with lidocaine and 248 ± 82 min (range 156–396) with lidocaine with epinephrine. The duration of motor blockade (MVAS score 8→8) was 48 ± 31 min (range 0–101) with lidocaine and 198 ± 81 min (range 125–372) with lidocaine with epinephrine.

After the local anesthetic injections, the SSEP

changes may be immediate, and abolition of the Erb's and C-7 amplitudes may occur on the first or second postblock SSEP testing. For example, in one volunteer, abolition of the Erb's and the C-7 amplitudes occurred 9 min after the block (Fig. 1). The cortical amplitudes in the volunteer, though markedly reduced, remained. The Erb's and C-7 amplitudes recovered at 72 min after the block. During complete sensory recovery, 104 min after the block, amplitudes of the Erb's, C-7 and cortex were 100, 79, and 69% of the baseline valves. Their respective prolongation of latencies were 22, 6, and 1%.

One of the subjects had a greater than 50% depression of the three amplitudes after saline injection (Table 1). The depression lasted 23 min for the Erb's point, 9 min for C-7, and 16 min for the cortex. The volunteer had SVAS scores that ranged from 0.3 to 0.8; this lasted throughout the study. This injection was the volunteer's first injection. She did not complain of paresthesia, pain, or discomfort after the injection, and hematoma was not observed at the injection site.

After injection of saline with epinephrine, one subject had a greater than 50% depression of the Erb's point and an SVAS score of 0.4. Both SSEP and SVAS change lasted 4 min. After lidocaine injections, seven of the eight volunteers had amplitude depressions greater than 50% at all recording sites. The remaining volunteer had 100% depression of the Erb's amplitude and 81% depression of the C-7, but at no time during the experiment were his cortical potentials decreased by 50% or more. After lidocaine with epinephrine injections, all the volunteers had amplitude decreases greater than 50% at all recording sites.

None of the volunteers had 15% or greater prolongation of their latencies after saline and saline with epinephrine injections (Table 1). With regards to the volunteer whose amplitudes were depressed over 50%

Table 2. Duration of Blockade[a] with Lidocaine and
Lidocaine with Epinephrine
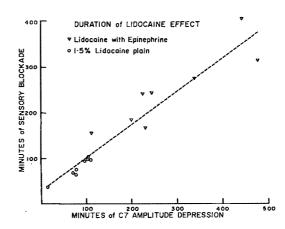
SSEP change[b]	Lidocaine	Lidocaine with epinephrine
Erb's point		
Amplitude	105 ± 21	324 ± 108
Latency	87 ± 33	258 ± 141
C7		
Amplitude	84 ± 27	289 ± 123
Latency	69 ± 49	200 ± 164
Cortex		
Amplitude	68 ± 35	245 ± 157
Latency	3 ± 7	53 ± 149
SVAS score[c]	83 ± 22	249 ± 82

[a]Minutes, mean ± SD.
[b]SSEP change = ≥50% decrease in amplitude and ≥15% prolongation in latency.
[c]Duration of SVAS score 8→8.

Figure 2. Comparison of the duration of sensory blockade as derived from the SVAS and depression of the C7 amplitude ($r = 0.96$).

after saline injection, the C-7 latency was increased by 14% for 7 min while the Erb's and cortical latencies were not prolonged at all. The volunteer who had a greater than 50% depression of his Erb's point amplitude after saline with epinephrine injection had no prolongation of the latencies of the three potentials. After lidocaine injections, all the volunteers had their Erb's point latencies prolonged by more than 15% (Table 1). Six of the eight volunteers had their C-7 latencies prolonged by more than 15%; the two remaining subjects both had their C-7 latencies prolonged by 13%. With regard to cortical latencies after lidocaine, only one had her cortical latency prolonged; the rest had prolongations that ranged from 6–10%. After lidocaine with epinephrine injections, all volunteers had greater than 15% prolongations of their Erb's point and C-7 latencies. However, only one had significant cortical prolongation; the remaining seven volunteers had prolongations of 7–12%.

The duration of nerve blockade by the lidocaine and lidocaine with epinephrine injections based on ≥50% depression of amplitude and ≥15% prolongation of latency is shown in Table 2. Using the duration of good block (SVAS scores of 8 or greater) as the dependent variable, MLR analysis showed ≥50% depression of C-7 as the best objective predictor of sensory blockade (sensory time = 0.73 C-7 amplitude +30; r = 0.96). The linearity was better with plain lidocaine than with lidocaine with epinephrine. The duration of ≥50% depression of the C-7 amplitude had a tendency to exceed the duration of the SVAS (Fig. 2).

With regard to the regression of the nerve blockade, the time to complete sensory recovery (SVAS 10 →0) was 118 ± 34 min (range 68–171) for lidocaine and 346 ± 171 min (range 181–717) for lidocaine with

epinephrine. The motor recovery, which preceded the sensory recovery, took 107 ± 39 min (range 65–171) for lidocaine and 339 ± 174 min (range 150–712) for lidocaine with epinephrine. At the time of complete sensory recovery, the depression of the SSEP amplitudes ranged from 0 to 67% while the latency prolongations ranged from 0 to 23% (Table 3).

Six of the eight volunteers had temperature increases after saline, whereas seven volunteers had temperature decreases after saline with epinephrine; the average temperature decrease was 3.1°C (range 1.9–4°C). None complained of paresthesia or showed signs of ischemia of the fifth finger. All volunteers had increases in skin temperature after lidocaine and lidocaine with epinephrine injections.

One volunteer, after a lidocaine with epinephrine injection, had paresthesias to her fifth finger for 5 days and pain and tenderness at the injection site for 1 week. The subsequent injection was done 19 days later. Two other volunteers had pain and tenderness that lasted 1–2 days. No other complications occurred.

Discussion

The objective evaluation of nerve blockade by different local anesthetics can be grouped into assessment of their effects on sympathetic, somatic motor, and somatic sensory function. Assessments of sympathetic blockade include measuring increases in temperature and pulse amplitude (12–14), use of the sympathogalvanic response (15), and sweat tests (16–18). Evaluation of motor blockade has been performed with electromyography (3). After ulnar nerve blocks, there is good correlation between hypothenar electromyography and the subjective evaluation of the muscle strength and motility of the fifth finger (3). Assess-

Table 3. Percentage Depression of Amplitude and Prolongation of Latency at the Time of Complete Sensory Recovery Measured at Three Sites

	Lidocaine	Lidocaine with epinephrine
Amplitude		
Erb's	22 ± 21 (0–67)	41 ± 29 (0–67)
C7	19 ± 14 (0–40)	8 ± 13 (0–27)
Cortex	16 ± 19 (0–55)	24 ± 23 (0–44)
Latency		
Erb's	13 ± 5 (7–22)	13 ± 7 (0–23)
C7	10 ± 6 (3–23)	7 ± 4 (0–15)
Cortex	4 ± 2 (1–7)	4 ± 2 (2–7)

All values are mean ± SD. Range is indicated in parentheses.

ment of the characteristics (onset, intensity, and duration) of motor blockade, however, does not give a true picture of the analgesic effect of a nerve blockade. Absence of significant motor blockade does not imply the absence of analgesia. In our study, after a lidocaine nerve block, one volunteer had a maximum MVAS score of 7 while his SVAS score was 10. Therefore, the study of the characteristics of sensory blockade provides a better evaluation of the analgesic properties of a nerve block.

The use of SSEP has been used to monitor the integrity of the spinal cord during operations on the spine (19). Median and ulnar nerve SSEPs have been utilized to confirm the diagnosis of thoracic outlet syndromes (20), and to study the ischemic effects of tourniquet (5). SSEP monitoring helped diagnose early brachial plexus injury in two patients: the observed changes were reversed by correction of the patients' positions (4). These studies suggest that SSEP monitoring should be able to objectively quantitate the occurrence and time course of a peripheral nerve blockade.

A 50% or greater depression of the amplitude is usually considered significant (11,19). A study in dogs concluded that "the spinal cord could tolerate sustained compression as long as the evoked spinal potentials were maintained at more than half their original amplitudes" (21). There has been no comparable study on the relationship between the magnitude of latency prolongation and neurologic dysfunction. Grundy et al. (11) chose a 4-msec or greater prolongation of the posterior tibial SSEP as significant, this being 10% of the average 40-sec latency in posterior tibial SSEPs. Because of the probable abnormality of nerve function after trauma (22), we selected a 15% or greater prolongation of latency as significant.

The duration of the depression of the C-7 amplitude was the best predictor of the time course of useful sensory blockade (SVAS score of 8 or more). Be-

cause the ulnar nerve is a mixed sensory and motor nerve, the depression of the Erb's amplitude and prolongation of its latency therefore did not correlate well with the sensory VAS scores. Although the measurements were made over the sensory cortex, the ability of the central nervous system to amplify nerve impulses compensates for peripheral axonal loss (23) so that a few remaining unblocked afferent fibers may be sufficient to evoke a sizable cortical SEP response (5). An incomplete peripheral nerve block may, therefore, not change the cortical potential significantly. The information gathered over the C-7 spinal cord gave the best correlation. Sensory, orthodromic information is mediated up the dorsal columns whereas antidromic motor information does not travel farther than the anterior horn at its level of entry (24). Because the amplitude of any volume conducted signal varies inversely as the square of the distance between the signal generators and the recording electrodes, the signals recorded over the posterior cervical cord should be almost exclusivly sensory in nature.

The duration of SVAS blockade induced by lidocaine in this study is in agreement with the findings of Poppers et al. (3). They found a duration (disappearance to complete reappearance of pain sensation) of 165 ± 21.8 min for 1% lidocaine and 379 ± 20.1 min for 1% lidocaine with epinephrine (3).

Recent studies suggest that epinephrine may have a local anesthetic effect of its own (6,7). In one study, T-10 to L-2 segmental hypalgesia for 6 hr was noted in one volunteer after the epidural administration of 50 μg epinephrine in 10 ml saline (7). Another study showed the suppression of noxiously evoked activity of wide dynamic range neurons (neurons associated with the central transmission of pain information) in the dorsal horn of the spinal cord in cats (8). The mechanism of epinephrine antinociceptive effect may be due to its interaction with the descending supraspinal pathways that are adrenergic in nature. Based on the absence of significant changes in the SSEP amplitude and latency, and in the SVAS scores, we conclude that epinephrine does not have a local anesthetic effect on the ulnar nerve. The difference between our results and those of others (7,8) may be due to the lack of influence of decending supraspinal noradrenergic pathways on a peripheral nerve setup. Although the possibility of an added local anesthetic effect of epinephrine in an isolated nerve preparation has been raised (25), the same investigators found minimal to no effect of the bisulfite-free epinephrine on the nerve action potential amplitude (26).

We ascribe the finding of decreased SSEP amplitudes after saline injection to nerve trauma. In our study, paresthesias were sought before each injection

to avoid clinical failures (onset more than 30 min or duration less than one hr for lidocaine) (3). Abnormal action potentials on the electroneurogram have been documented after nerve trauma (22). The persistence of greater than 50% depression of the amplitude and greater than 15% prolongation of latencies in some of our volunteers (Table 3) after complete sensory recovery (SVAS score of 0) supports this possibility.

The decreases in temperature after saline with epinephrine may be due to diffusion of the drug into the area of the ulnar artery, which is located at the medial side of the elbow, near the ulnar groove (27). This could have caused constriction of the artery and its palmar digital arteries.

In summary we conclude that ulnar nerve SSEP monitoring provides an objective evaluation of ulnar nerve local anesthetic blockade. Of three possible sites, monitoring at the cervical level provides the best correlation of the duration of "good sensory blockade." Finally, based on the sensory VAS and SSEP monitoring, we conclude that epinephrine does not have a local anesthetic effect on a peripheral nerve.

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Dose-Related Cardiovascular Effects of Amrinone during Enflurane Anesthesia in the Dog

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The dose-related cardiovascular effects of amrinone, a synthetic cardiotonic and vasodilating drug, were investigated in dogs anesthetized with enflurane (2.2–2.4% end-tidal concentration). Twelve mongrel dogs were divided into two groups of six animals: an enflurane group (E) that received only enflurane, and an amrinone group (A). In the latter group each dog received the following sequential boluses and 30-min infusions: 1) the amrinone solvent alone; 2) amrinone, 1 mg/kg + 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$; 3) amrinone, 2 mg/kg + 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$; 4) amrinone, 4 mg/kg + 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Over the course of the experiment, 2.2–2.4% end-tidal enflurane alone resulted in a gradual decrease in cardiac index (CI), stroke volume index (SVI), and the maximum left ventricular dP/dt (LV dP/dt_{max}), without changes in heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), or pulmonary capillary wedge pressure (PCWP) in group E. Significant differences from group E after 30 min of the lowest dose of amrinone included higher CI and SVI with lower systemic vascular resistance (SVR). The medium dose of amrinone, in addition to the effects already observed with the lowest dose of amrinone, decreased MAP and pulmonary vascular resistance (PVR), and increased LV dP/dt_{max}, when compared to group E only. Furthermore, the highest dose of amrinone caused lower pulmonary artery mean pressure (PAM), PCWP, and higher HR with shortened PR interval. The differences in MAP, CI, LV dP/dt_{max}, PCWP, PAM, PR interval, SVR, and PVR compared to E were still significant 30 min after the cessation of the highest dose. This study shows that the myocardial depressant effects of enflurane in an unstimulated canine model with a previously healthy heart can be overcome in a dose-related manner by amrinone. In contrast to other vasodilators, no reflex increase in plasma catecholamines was seen. Improvements in cardiac performance occurred at plasma levels of amrinone below those at which significant decreases in MAP attributable to amrinone were seen.

Amrinone, a synthetic cardiotonic drug with vasodilating activity, is a bipyridine derivative unrelated to either the digitalis glycosides or catecholamines. Amrinone has a rapid onset of action, long duration, and wide therapeutic index when compared with digitalis glycosides or catecholamines (1). It is remarkably free of adverse reactions (2).

Single-dose and short-term oral and intravenous studies in unanesthetized subjects show dose-related improvements in cardiac index (CI) and left ventricular stroke work index, as well as substantial decreases in pulmonary capillary wedge pressure (PCWP), pulmonary artery mean pressure (PAM), and right atrial pressure (RA), with only insignificant effects on mean arterial pressure (MAP) or heart rate (HR) (3–6).

Hayes et al. suggested that the inotropic properties of amrinone derive from its capacity to increase the intracellular concentration of Ca^{2+} and cyclic adenosine monophosphate (cAMP) (7). In 1982, Kariya et al. demonstrated that amrinone selectively inhibits phosphodiesterase fraction III (PDE III). With the inhibition of PDE III, cAMP breakdown is reduced (8). The augmented myocardial cAMP content potentiates Ca^{2+} delivery to the contractile system.

So far amrinone has been used clinically only in the treatment of severely disabling congestive heart failure refractory to conventional therapy. Significant beneficial effects have been noted in patients treated with amrinone soon after open heart surgery (9) and also when joint administration of amrinone and hydralazine or amrinone and dobutamine have been used (10).

Patients may receive amrinone in the perioperative period. Thus a better understanding of its interactions with anesthetics is important because inhalation anesthetics themselves cause dose-related depression of cardiac function (11–13). This study was designed to determine the dose-related cardiovascular effects of amrinone in the presence of the potent inhalation anesthetic enflurane.

Methods

Twelve conditioned mongrel dogs of either sex, weighing 22 ± 1 kg (mean ± SEM) with chronic tracheostomies were anesthetized with enflurane (2.2–2.4% end-tidal) in 40% oxygen in air, and mechanically ventilated (Harvard Apparatus Company, Model 623) to maintain pH and $Paco_2$ within normal limits. Adequate hydration and urine output were maintained with intravenous NaCl, 0.9%, at approximately 10 ml·kg^{-1}·h^{-1}. Normothermia was maintained with a warming blanket and a heating lamp. The end-tidal concentrations of enflurane, CO_2, and O_2 were continuously measured by mass spectrometry (Perkin-Elmer, Model MGA 1100). An arterial catheter was placed in the femoral artery for direct blood pressure measurements and plasma sampling. A pulmonary artery catheter was passed via an external jugular vein for measurements of RA, PAM, and PCWP, and determination of cardiac output (CO) in triplicate by thermodilution (Edwards Laboratories cardiac output computer, Model 9520). A micromanometer-tipped catheter (Millar Instruments, Inc., Model PC 350) was placed retrograde in the left ventricle (LV) via a femoral artery for direct left ventricular pressure measurements and electronic derivation of left ventricular dP/dt (LV dP/dt). Limb lead II of the electrocardiogram (ECG), HR, arterial blood pressure, CVP, pulmonary artery pressure, LV pressure, and LV dP/dt were continuously recorded on a Hewlett-Packard polygraph, Model 7758A. The ECG was intermittently recorded at fast paper speed (100 mm/sec) for measurement of PR intervals. The maximum LV dP/dt (LV dP/dt$_{max}$) was taken as the peak positive deflection of the LV dP/dt trace. The plasma samples were analyzed for epinephrine (EPI), norepinephrine (NE), and amrinone by high performance liquid chromatography (14,15). Systemic and pulmonary vascular resistances (SVR, PVR), CI, and stroke volume index (SVI) were calculated.

The animals were divided into two groups of six dogs: an enflurane group (E) that received only enflurane, and an amrinone group (A). After 60 min of stabilization on the anesthetic, baseline measurements were made and plasma samples taken in both groups, which were repeated every 30 min in group E. In group A, amrinone freshly dissolved in the sol-
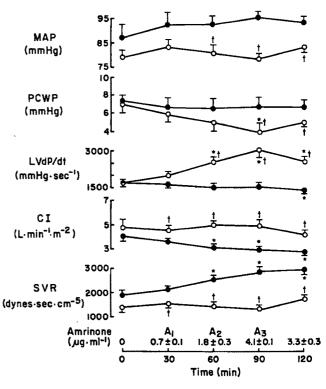
Figure 1. Hemodynamic measurements in the amrinone–enflurane group (O), and in the enflurane only group (●). Data are expressed as mean ± SEM. Symbols: *P < 0.05 compared to time zero. †P < 0.05 when the amrinone–enflurane group was compared to the enflurane only group. A₁, A₂, and A₃ are the different successive bolus and infusion rates of amrinone (see text).

vent for each experiment was given in the following sequential boluses and 30-min infusions (IVAC 230 infusion pump, IVAC Corporation): 1) the amrinone solvent alone (in an amount equivalent to that used for the largest bolus and the largest 30-min infusion of amrinone given (A₃)); 2) A₁, 1 mg/kg + 5 μg·kg^{-1}·min^{-1}; 3) A₂, 2 mg/kg + 10 μg·kg^{-1}·min^{-1}; 4) A₃, 4 mg/kg + 20 μg·kg^{-1}·min^{-1}. The bolus of amrinone was injected over 2 min, and the infusion was started at the same time. Cardiovascular measurements and plasma samples were taken at 25 and 30 min after beginning each infusion in group A and also 30 min after discontinuation of the A₃ infusion. Blood samples for measurement of serum levels of potassium, sodium, calcium, chloride, and glucose were taken three times during each experiment: at baseline, 60 min after beginning amrinone, and at the time of the final measurements.

Changes within each group were analyzed by analysis of variance for repeated measures. The Bonferroni modified t-test was used when analysis of variance for repeated measures indicated significant differences. A non-paired t-test was used to compare the results between group A and group E. A P value of less than 0.05 was considered statistically significant.
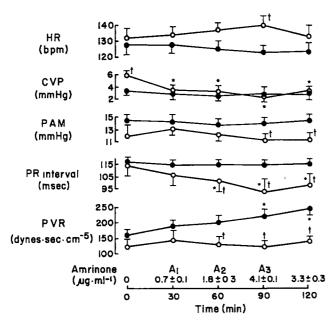
Figure 2. Hemodynamic measurements in the amrinone–enflurane group (O), and in the enflurane only group (●). Data are expressed as mean ± SEM. Symbols: *P < 0.05 compared to time zero. †P < 0.05 when the amrinone–enflurane group was compared to the enflurane only group. A₁, A₂, and A₃ are the different successive bolus and infusion rates of amrinone (see text).

Figure 3. Epinephrine (EPI) and norepinephrine (NE) values in the amrinone–enflurane group (O), and in the enflurane only group (●). Data are expressed as mean ± SEM. Symbols: *P < 0.05 compared to time zero. There were no differences between the two groups. A₁, A₂, and A₃ are the different successive bolus and infusion rates of amrinone (see text).

Results

There were no significant effects from the solvent alone in group A. There were no differences between the 25- and 30-min values for any variable during any of the infusions of amrinone. Control (time zero) and values at 30-min intervals for the groups A and E are shown for MAP, PCWP, LV dP/dt_{max}, CI, and SVR in Figure 1, and for HR, CVP, PAM, PR interval, and PVR in Figure 2. For clarity, plasma amrinone levels for group A at 30 min of each infusion are given in both Figures 1 and 2. Enflurane alone at end-tidal concentrations of 2.2–2.4% resulted in significant decreases in CI and SVI and later increases in SVR and PVR with a decrease in LV dP/dt_{max} after 120 min. There were no changes in HR, MAP, PAM, CVP, PCWP, or PR interval compared to time zero in the E only dogs. At time zero there was no difference between groups A and E except for a higher CVP in group A. Significant differences from E after 30 min of A₁ (amrinone plasma level = 0.7 ± 0.1 μg/ml) included higher CI and SVI with lower SVR. Differences from E after 30 min of A₂ (amrinone plasma level = 1.8 ± 0.3 μg/ml), in addition to those effects observed with A₁, also included lower MAP and PVR, and higher LV dP/dt_{max}. Furthermore, A₃ (amrinone plasma level = 4.1 ± 0.1 μg/ml) caused lower PAM, PCWP, and higher HR with a shortened PR interval. The differences in MAP, CI, LV dP/dt_{max}, PCWP, PAM, PR interval, SVR, and PVR compared to E were still

significant 30 min after the cessation of A₃ when the amrinone plasma level was 3.3 ± 0.3 μg/ml (Figs. 1 and 2). No significant differences were observed between groups E and A in plasma levels of EPI or NE, which are shown in Figure 3. Serum electrolytes (potassium, sodium, calcium, and chloride), glucose, and hematocrit were all within normal limits throughout the study in all the dogs.

Discussion

This study has shown the dose-related effects of amrinone in effecting improvement of hemodynamic function in the presence of anesthetic concentrations of enflurane. These findings were observed in unstimulated animals with previously healthy hearts in the absence of other pharmacologic interventions.

In conscious dogs and in dogs with pentobarbital-induced heart failure, Alousi et al. demonstrated that amrinone bolus injections and intravenous infusions significantly increased LV dP/dt with small changes in HR and blood pressure (1). Boncyk et al. studied hemodynamic effects of amrinone in dogs anesthetized with halothane and compared amrinone with isoproterenol and dobutamine. They used relatively high concentrations of halothane and administered large doses of amrinone to fully overcome the depressant effects of large doses of halothane upon CO; however such doses resulted in very low blood pressures in the amrinone-treated animals compared to the dobutamine group (16). In our study, improvement in cardiac performance occurred at plasma levels of amrinone below those at which significant decreases in MAP attributable to amrinone were seen.

In patients with congestive heart failure, a direct linear correlation has been observed between the increase in CI and amrinone plasma concentration (5).

During enflurane anesthesia, the doses of amrinone given in the present study did not cause a significant change in CI or SVR compared to time zero, however when compared to enflurane alone, amrinone did show plasma level-related effects. At plasma levels of less than 1 μg/kg, amrinone increased CI and SVI and decreased SVR compared to enflurane, whereas at plasma levels of approximately 4 μg/ml, in addition to increased CI and SVI, amrinone also increased HR, shortened PR interval, increased LV dP/dt_{max}, and decreased MAP, PAM, PCWP, and PVR. The comparison of an enflurane only control group was an important factor in the design of this study to account for changes in the preparation with time with the anesthetic alone.

The electrophysiologic effects of amrinone have been studied in patients with congestive heart failure by Goldstein et al. They concluded that amrinone does not appear to have significant arrhythmogenic potential during acute administration (17). It has been reported that the increase in HR associated with amrinone was dose related in anesthetized and conscious dogs (6). In our study, only the largest dose of amrinone caused a significant increase in HR and a significant shortening of PR interval which was still significant 30 min after the cessation of A₃. However, baseline heart rates are elevated in anesthetized dogs compared to awake heart rates, which are usually less than 100 beats/min (18,19). No arrhythmias were observed. This increase in HR cannot be attributed to reflex sympathetic activation, because in contrast to other vasodilators no increase in plasma catecholamines was seen (Fig. 3). The mechanism of action of amrinone is different from that of sympathomimetic amines. Its inotropic, chronotropic, and peripheral vasodilatory actions are mediated primarily by selective inhibition of PDE III, and a direct effect to increase heart rate can be expected. At high doses, alterations in calcium transport may also contribute to its effect (9).

Our study has shown that amrinone had a beneficial effect on the cardiac depression caused by 2.2–2.4% end-tidal concentrations of enflurane in the dog. There was a strong correlation between amrinone plasma concentrations and improvement in cardiac performance without increase in plasma catecholamines. At amrinone plasma levels of approximately 3–4 μg/ml, there was an enhancement in atrioventricular conduction without any arrhythmias. Although the extrapolation of results obtained from animal studies to humans is limited, this study indicates that amrinone may be a useful agent to improve cardiac performance in the perioperative period, even in the presence of potent inhalation anesthetics.

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The Extra Work of Breathing Through Adult Endotracheal Tubes

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BOLDER PM, HEALY TEJ, BOLDER AR, BEATTY PCW, KAY B. The extra work of breathing through adult endotracheal tubes. Anesth Analg 1986;65:853-9.

A sinusoidal flow generator was connected to adult endotracheal tubes of sizes 5-10 and was used to simulate human ventilation. Measurement of the changes in pressure and flow allowed calculation of the work imposed on breathing

by endotracheal tubes. The work of breathing increased with increasing ventilatory rate, tidal volume, and decreasing tube diameter. We discuss the suggestion that the work imposed on breathing by an endotracheal tube is a more appropriate unit for comparison than resistance to air flow.

Key Words: INTUBATION—tracheal. VENTILA-TION—work of. EQUIPMENT, TUBES—tracheal.

The method of obliging a person to get all the air through tubes and valves, which is essential to success in the inhalation of ether, is perfectly new, and . . . greater facilities for respiration are required than would generally have been supposed. On this account, many of the apparatuses at first invented did not allow for easy respiration, but offered obstruction to it—by sponges, by the ether itself, by valves of insufficient size, but more particularly by tubes of too narrow calibre; and there is reason to believe that . . . . this was a cause of failure (1).

These prescient observations were written by John Snow in 1847, only one year after the first demonstration of ether anesthesia. Traditionally, components of anesthetic equipment have been analyzed functionally in terms of their resistance to steady gas flow. However, anesthetics are always administered under continually changing flow conditions, which may include a degree of turbulence. It would therefore be more appropriate to compare the additional work imposed on breathing by a component of the circuit rather than the effects of the component on the resistance to air flow.

Atlan et al. measured the work of breathing through endotracheal tubes using oscillatory flow, but they did not specify the ventilatory waveform employed (2). Most of their data were obtained at relatively high minute ventilations, and only for endotracheal tube

sizes 7.5, 8.0, 9.0, and 10.0. They did not assess the work of breathing when ventilatory rate and tidal volume were varied independently.

The additional work of breathing through a breathing system can be measured experimentally when gas with a sinusoidal flow pattern is driven through it (3). This method has been used to compare the mechanical efficiency of various anesthesia circuits (4). However, the contribution of an endotracheal tube to the work of breathing has not been examined using this technique. The aim of this study was to compare endotracheal tubes of different sizes and to examine the suitability of using the extra work involved in breathing through them for this comparison.
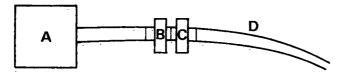
Methods

A simple mechanical pump generated flow at "respiratory rates" of 6, 12, and 20 per minute. Three cams alternately drove the pump, delivering tidal volumes of 350, 500, or 900 ml in a sinusoidal pattern that was checked using a pneumotachograph.

The flow generated by the pump was measured using a Fleisch No. 2 pneumotachograph and a micromanometer placed immediately proximal to the endotracheal tube. Pressure was measured at the entrance to the endotracheal tube, through a 19-gauge needle, with a flat tip inserted into the 15 mm connector and attached to a Statham P50 pressure transducer. The pressure drop across the endotracheal tube (P) was taken as the difference between the pressure at the entrance of the endotracheal tube and atmospheric pressure, the distal end of the tube being unobstructed and open to the atmosphere. Before each experiment, the pneumotachograph was calibrated

Figure 1. Diagrammatic representation of the apparatus: A, Si-nusoidal flow generator; B, Fleisch pneumotachograph; C, pressure transducer; D, endotracheal tube.

Figure 2. A pressure-volume loop, idealized.

with 100% oxygen from a dry gas meter calibrated using a bubble flow meter, and the pressure transducer was calibrated with a water manometer. Figure 1 depicts the experimental apparatus.

Pressure and flow measurements were recorded simultaneously using a Grass Polygraph and a Tandberg 1600 S3 analog tape recorder. Recorded data were then processed with a Data General Nova II computer, which sampled the data at 50-sec intervals, integrated flow data to yield volume, and then plotted a pressure-volume loop, which is shown in idealized form in Figure 2. The work being dissipated is equal to the area contained between any relevant part of the P/V plot and the volume axis (4). The areas were measured using an Apple II microcomputer and graphics tablet. These areas represent work, because the work (W) done in driving a volume (V) across a tube is equal to the integral of the product of the pressure drop across the tube (P) and the flow (dV/dt) (5).

$$W = \int P dV$$

The use of the graphics tablet to measure work entails manually tracing the pressure-volume loops. Each loop was traced ten times. The mean values and the SEMs were calculated. The mean values obtained in each of the 54 experimental conditions are given in Tables 1-3.

Uncut Mallinckrodt "high-lo" endotracheal tubes, sizes 5.0, 6.0, 7.0, 8.0, 9.0, and 10.0, were used with the cuffs deflated. Measurements were made with the tubes in their preformed, slightly curved shape.

All measurements were made in a centrally heated laboratory. No corrections were made for any fluctuations in barometric pressure, temperature or humidity, or for the fact that the pneumotachograph was calibrated with 100% oxygen instead of air.

All references to diameter and radius refer to inner diameter and inner radius, respectively.

Results

The mean values obtained in each of the 54 experimental conditions are given in Tables 1-3. The SEMs ranged from 0.157 to 5.03 mJ.
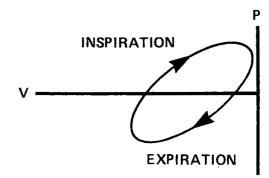
The measurement threshold in our experimental apparatus was approximately 2.5 mJ. This threshold was not reached in two of our experimental conditions: a ventilatory rate of 6 and tidal volume of 350 for tube sizes 9 and 10.

Our data shows that work increases whenever endotracheal tube diameter decreases, ventilatory rate increases or tidal volume increases. The difference in the magnitude of extra work incurred by a change in tube size was greatest when small tubes were compared.

The data have been organized into nine sets and graphically presented in Figure 3. Each set represents a fixed tidal volume and ventilatory rate. Eight of the sets contain six data points; the remaining set consists of only four, because in two of the conditions the work was equal to the measurement threshold. Each set may be fitted to a straight line, the logarithmic form of the relation $W = ar^{-b}$

$$\log W = \log a - b \log r$$

where W is work per minute (mJ/min) and r is the tube radius in cm. The values for a and b may be calculated by least squares fitting and are shown in Table 4.

Maximum flow rates ($\dot{V}_{max}$), Reynolds numbers (Re), and Womersley numbers (α) are also given in Tables 1-3 and were calculated using the following formulae:

$$\dot{V}_{max} = \pi R V_T/60$$
$$Re = (2\rho/\pi)(dV/r\eta)$$
$$\alpha = r[(2\pi/60)(R\rho/\eta)]^{\frac{1}{2}}$$

The constants for viscosity (η) and density (ρ) for dry air at 18°C and 760 mm Hg pressure were obtained from the Handbook of Chemistry and Physics (6):

$$\eta = 1.827 \times 10^{-4} \text{ poise}$$
$$\rho = 1.213 \times 10^{-3} \text{ g/cm}$$

Table 1. Experimental Data and Calculated Parameters at a Ventilatory Rate of 6/min

VT (ml)	$\dot{V}_{max}$ (ml/sec)	Diameter (mm) (D)	Reynolds number (Re)	Womersley number (α)	Work/breath (mJ) (W_B)	Work/min (mJ/min) (W_{min})
350	110	5.0	1860	0.51	50	298
		6.0	1550	0.61	26	158
		7.0	1328	0.71	10	62
		8.0	1162	0.82	8	47
		9.0	1033	0.92	—	—
		10.0	930	1.02	—	—
500	157	5.0	2654	0.51	157	944
		6.0	2212	0.61	82	491
		7.0	1896	0.71	46	278
		8.0	1659	0.82	34	206
		9.0	1475	0.92	23	140
		10.0	1327	1.02	11	68
900	283	5.0	4785	0.51	383	2299
		6.0	3987	0.61	205	1231
		7.0	3418	0.71	114	685
		8.0	2990	0.82	87	519
		9.0	2658	0.92	58	350
		10.0	2391	1.02	29	171

Abbreviations: VT, tidal volume; $\dot{V}_{max}$, maximum flow velocity; Diameter, internal diameter of endotracheal tube.

Discussion

Many anesthesiologists assume that endotracheal intubation imposes a burden on the spontaneously breathing patient. This belief has led some to advocate the routine use of the largest possible endotracheal tubes—even sizes with diameters greater than 14 mm (7).

Although the physiologic effects of endotracheal intubation are frequently discussed in terms of the work they impose on the patient, they have nearly always been investigated by determining the resistance to air flow. The Hagen–Poiseuille equation states that resistance varies inversely with the fourth power of the tube radius, thus confirming the intuition that decreasing tube diameter greatly increases air flow resistance. However, this relation applies only to laminar flow. At gas flows and tube diameters used clinically, the flow is usually assumed to be turbulent (8). Reynolds numbers are used to classify flow as laminar, transitional, or turbulent. When Reynolds numbers are calculated as part of clinically relevant resistance experiments, they usually indicate that flow is nonlaminar (9). Therefore, the resistance of endotracheal tubes and other anesthesia equipment must be determined empirically.

Values for the resistances of endotracheal tubes have been reported (10,11), and differences in the values have been attributed to differing experimental methods (12). However, although the magnitude of the measured tube resistances may vary between studies, the results are qualitatively similar. Each millimeter decrease in tube size is accompanied by a large increase in resistance, in the range of 25–100%. With increasing gas flows, resistance also increases, but nonlinearly.

Our results reveal that the increase in the work of breathing with decreasing tube size parallels the change in resistance because they are both functions of pressure. A 1-mm decrease in tube size results in an increase in work of 34–154%, depending on the ventilatory rate and tidal volume. Increasing the ventilatory rate and increasing tidal volume are essentially different techniques for increasing flow; both methods were associated with large increases in work.

We have calculated Reynolds numbers at the maximum velocity of the sinusoidal flow for each type of ventilatory cycle studied. Conventionally, a Reynolds number of 2000 is said to indicate the point at which flow ceases to be laminar. In our experiments, 43 of 54 Reynolds numbers were over 2000.

Unfortunately, the use of Reynolds numbers to describe flow through endotracheal tubes is neither straightforward nor determinate. Curvature must be considered, because the amount of turbulence in tubes is affected by their geometry. Curving a tube may actually allow flow to remain laminar at Reynolds numbers, which would suggest the presence of turbulence in a straight tube (13). This may explain why curving an endotracheal tube by up to 90° has been found to increase resistance by only 3% (9).

Further complexity is introduced when oscillatory

Table 2. Experimental Data and Calculated Parameters at a Ventilatory Rate of 12/min

V_T (ml)	$\dot{V}_{max}$ (ml/sec)	Diameter (mm) (D)	Reynolds number (RE)	Womersley (α)	Work/breath (mJ)	Work/min (mJ) (W_{min})
350	220	5.0	3720	0.72	229	2743
		6.0	3100	0.87	118	1415
		7.0	2657	1.01	69	833
		8.0	2325	1.16	44	528
		9.0	2066	1.30	30	355
		10.0	1860	1.44	18	215
500	314	5.0	5309	0.72	450	5402
		6.0	4424	0.87	249	2993
		7.0	3792	1.01	141	1692
		8.0	3318	1.16	84	1013
		9.0	2949	1.30	63	760
		10.0	2654	1.44	33	392
900	566	5.0	9569	0.72	1091	13097
		6.0	7974	0.87	619	7529
		7.0	6835	1.01	347	4158
		8.0	5981	1.16	215	2578
		9.0	5316	1.30	152	1818
		10.0	4785	1.44	80	959

Abbreviations: V_T, tidal volume; $\dot{V}_{max}$, maximum flow velocity; Diameter, internal diameter of endotracheal tube.

Table 3. Experimental Data and Calculated Parameters at a Ventilatory Rate of 20/min
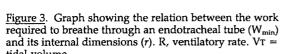
V_T (ml)	$\dot{V}_{max}$ (ml/sec)	Diameter (mm) (D)	Reynolds number (Re)	Womersley number (α)	Work/breath (mJ) (W_B)	Work/min (mJ) (W_{min})
350	367	5.0	6205	0.93	332	6630
		6.0	5171	1.12	216	4318
		7.0	4432	1.31	138	2754
		8.0	3878	1.49	88	1764
		9.0	3447	1.68	62	1240
		10.0	3102	1.86	31	618
500	524	5.0	8859	0.93	814	16282
		6.0	7383	1.12	526	10518
		7.0	6328	1.31	306	6116
		8.0	5537	1.49	212	4232
		9.0	4922	1.68	150	3002
		10.0	4430	1.86	65	1298
900	943	5.0	15943	0.93	1560	31198
		6.0	13286	1.12	1140	22800
		7.0	11388	1.31	700	13990
		8.0	9964	1.49	505	10106
		9.0	8857	1.68	350	7000
		10.0	7972	1.86	175	3506

Abbreviations: V_T, tidal volume; $\dot{V}_{max}$, maximum flow velocity; Diameter, internal diameter of endotracheal tube.

rather than constant flow is considered, because the Reynolds number was derived for application to constant flow. Another dimensionless parameter (called the Womersley number by some) is said to characterize oscillatory flow and can be used in a manner analogous to the use of Reynolds numbers for steady flow. At Womersley numbers of the order one or below, inertial rather than viscous effects predominate,

so that the flow may be considered "quasi-steady" (14,15). We have calculated Womersley numbers for each of our experiments, and all of these numbers are of the order one.

Most studies of oscillatory flow have attempted to model human airways or blood vessels, usually at high frequencies. Atlan et al. (2) used oscillatory flow to measure the work of breathing through endotra-

Figure 3. Graph showing the relation between the work required to breathe through an endotracheal tube (W_{min}) and its internal dimensions (r). R, ventilatory rate. V_T = tidal volume.

R		V_T
▲	20	900
△	20	500
■	12	900
□	20	350
×	12	500
○	12	350
●	6	900
+	6	500
◊	6	350

cheal tubes at a respiratory rate of 24 breaths/min, a frequency occasionally used clinically. Their methodology differed slightly from ours in that they attached a balloon to the end of the endotracheal tube and also used only one ventilatory rate; therefore our results are not exactly comparable. They reported that for a size 8 tube the work was of the order of 0.1 Watts when the ventilation was 12 L/min with a frequency of 24. We obtained a value for work of 0.07 Watts under our nearest comparable experimental condition (size 8 tube, rate of 20 breaths/min, and tidal volume of 500 ml). The experiment described by Atlan et al.

would be expected to result in a greater work of breathing than that reported in the present study because the ventilatory rate and minute ventilation were higher. However if the differences are taken into account, the data from these two studies are essentially in agreement.

Work of breathing can be measured in patients who are breathing spontaneously through an endotracheal tube. Flow and pressure are measured at the entrance of the endotracheal tube. The second pressure measurement is taken from an esophageal balloon, which estimates intrapleural pressure. This technique has

Table 4. Coefficients of the Expression $W = ar^{-b}$ Determined by Least Squares Fittings to Form log $W = \log a - b \log r$

Ventilatory rate	V$_T$	b	a
6	350	4.1512	0.9563
	500	3.5455	7.061
	900	3.5115	18.18
12	350	3.5861	19.16
	500	3.6624	35.44
	900	3.6645	86.90
20	350	3.2829	79.56
	500	3.4276	160.6
	900	3.018	554.7

Abbreviation: V$_T$, tidal volume

been employed in infants to correlate increases in air flow resistance with increases in the work of breathing, when endotracheal tube size was decreased by 1.5 mm (16). This decrease in endotracheal tube diameter increased resistance by an average of 226% during each breath, whereas work per breath increased 205%. Blood gases did not change in any of the infants studied after the resistance was increased. Because the respiratory muscles normally require only about 2% of the total oxygen consumption, it is not surprising that respiratory work can double without functional decompensation (17).

However, critically ill patients may be unable to tolerate even relatively small increases in the work of breathing. Several investigators have suggested that measured respiratory work can predict the likelihood of successful "weaning" from mechanical ventilation. Henning et al. (18) found that patients with obstructive airway disease remained dependent on mechanical ventilation if their work of breathing was greater than or equal to 1.7 kg m/min (0.27 Watts). Proctor and Woolson studied postoperative patients and reported that a work of breathing of 2.50 kg·m·min^{-1} (0.41 Watts) distinguished between those who were successfully "weaned" and those who needed continued ventilatory support (19). They also stated that the normal work of breathing in young men is 0.442 kg·m·min^{-1} (0.072 Watts).

If the normal work of breathing is approximately 0.07 Watts, does the insertion of an 8.0-mm endotracheal tube double the work of breathing? This conclusion might be inferred from our data, because "breathing" through an 8.0-mm tube with V$_T$ = 500 and R = 20 resulted in a value for the work of breathing of 0.07 Watts. However, such an interpretation must be made with caution. The endotracheal tube does not simply increase resistance, and hence work; it replaces the normal upper airway resistance. Upper

airway resistance can be physiologically advantageous during expiration, as exemplified by preferential nasal breathing by neonates, the "grunting" of neonates with respiratory distress, and the "pursed lips" breathing of adults with pulmonary disease. Some researchers have even argued that tracheotomy cannulae should be designed so as to mimic normal upper airway resistance (20).

Colgan et al. studied respiratory mechanics, blood gases, and intrapulmonary shunting in patients before and after removal of endotracheal tubes (21). The presence of an endotracheal tube had no effect on any of these variables. They proposed, using theoretical considerations, that endotracheal tubes would only impose a resistance significantly greater than that of the normal airway if the patient's ventilation was abnormally high. That a fixed upper airway obstruction is well-tolerated during resting minute ventilation was discussed by Nunn et al. in 1961 (22), who pointed out that patients with laryngeal cancer or subglottic stenosis endure extreme upper airway narrowing, provided their minute ventilation is normal. However, if panic occurs, an increased minute ventilation may cause a precipitous deterioration in respiratory function. Gal et al. demonstrated that in awake healthy volunteers, endotracheal intubation was followed by diffuse airway constriction producing an average increase in airways resistance of 141% (23). Vagally mediated airway responses probably underlie this phenomenon.

The work of breathing through endotracheal tubes thus may be influenced by the physical nature of the tube and by the patient's response to it. The measurements made here relate to the physical factors affecting tube resistance; in conscious patients other variables must be considered.

The results reported are consistent with the results obtained from conventional flow resistance testing. However, by allowing comparisons to be made with work incurred in other conditions, the results provide clinically relevant data, thereby supporting the view that for comparison of endotracheal tubes of different sizes work is a more appropriate measurement than resistance.

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Ketamine–Atracurium by Continuous Infusion as the Sole Anesthetic for Pulmonary Surgery

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REES DI, HOWELL ML. Ketamine–atracurium by continuous infusion as the sole anesthetic for pulmonary surgery. Anesth Analg 1986;65:860-4.

Fifty patients undergoing elective pulmonary resection were studied to evaluate the effects of the infusion of the combination of ketamine ($2 \ mg \cdot kg^{-1} \cdot hr^{-1}$) combined with atracurium ($0.6 \ mg \cdot kg^{-1} \cdot hr^{-1}$) on heart rate (HR), mean arterial pressure (MAP), neuromuscular block (NMB) and patient acceptability. Induction of anesthesia was accomplished in all patients within 45 sec. Statistically significant increases ($P < 0.01$) in MAP and HR occurred only after bronchoscopy and tracheal intubation (mean 12 mm Hg and 6 beats/min, respectively), subsequently returning to preinduction levels and remaining stable. The degree of NMB once established remained constant in each patient, 86% maintaining 1–4 twitches throughout surgery. Reversal of neuromuscular blockade was achieved within 10 min of antagonist drug administration in all but one patient. Recovery from anesthesia occurred within 30 min (mean <15 min) in all but 3 patients (all over age 60) and was independent of weight. No emergence phenomena were observed. We conclude that ketamine–atracurium fixed-rate combined infusion anesthesia provides good operating conditions and neuromuscular relaxation, cardiovascular stability, patient acceptability, and no significant side effects in patients undergoing pulmonary resections.

Key Words: ANESTHETICS, INTRAVENOUS—ketamine. ANESTHETIC TECHNIQUES—intravenous.

Ketamine hydrochloride, introduced into anesthetic practice after the clinical studies of Domino et al. (1) is an anesthetic that can be administered by intramuscular injection, intravenous bolus injection, or continuous intravenous infusion. Ketamine is well-established as an anesthetic for various surgical procedures, as is its use as a continuous infusion with or without nitrous oxide (2–7).

Atracurium besylate, a recently introduced competitive depolarizing neuromuscular blocker, has a relatively short duration of action, is noncumulative, and is remarkably free of cardiovascular side effects even after repeated injections (8). These properties make atracurium eminently suitable for administration by continuous infusion (9–11).

The continuous infusion of anesthetic drugs confers several theoretical and practical advantages over intermittent bolus injections. These include the elimination of abrupt changes in serum levels of drugs frequently associated with intermittent bolus injections, thus giving rise to more stable serum, and hence, brain concentrations of the anesthetic drug infused. Theoretically, the intravenous infusion of a drug can produce an anesthetic course akin to that obtained by the administration of inhalational anesthetics. Other advantages of the continuous infusion of drugs as opposed to intermittent bolus injection include decreased drug requirements with the continuous infusion technique and a more rapid rate of recovery from anesthesia (6).

The purpose of this clinical study was to evaluate the feasibility of the combined continuous infusion of ketamine and atracurium in a fixed dose ratio infusion as the sole anesthetic for pulmonary surgery. Surgical operating conditions, intraoperative cardiovascular stability, time to recovery from anesthesia and neuromuscular block, and the incidence of side effects were investigated.

Methods

Fifty adult men ASA class II or III undergoing thoracotomies for resection of intrathoracic tumors were studied. Patients ranged in age from 35 to 70 yr; all gave informed consent. The study met institutional guidelines. All patients were evaluated preoperatively and were premedicated in the operating room with diazepam, 10 mg, and droperidol, 5 mg intra-

Table 1. Perioperative Cardiovascular Data[a]

	Number of patients	Preinduction value	After bronchoscopy/intubation	Time from induction (min)		
				60	90	120
MAP (mm Hg)	50	98 ± 2.0	110 ± 2.3[b]	100 ± 2.6	95 ± 2.2	95 ± 2.4
Heart rate (beats/min)	50	81 ± 1.4	87 ± 2.1[b]	83 ± 1.8	84 ± 1.8	84 ± 1.7

[a]Mean ± SEM.
[b]Statistically significantly different from preinduction values ($P < 0.01$).

venously, after establishment of an intravenous infusion. Monitoring consisted of a continuously displayed ECG and radial artery pressure from an indwelling 20 gauge 2″ Abbocath. Both ECG and arterial pressure traces were displayed using a Siemens Sirecust 404 system.

Induction of anesthesia was effected by a bolus intravenous injection of ketamine, 2 mg/kg, and muscle relaxation attained with the intravenous administration of atracurium, 0.5 mg/kg. After induction, all patients underwent bronchoscopy followed by laryngoscopy and tracheal intubation using a right or left Robertshaw endobronchial tube, as indicated by the site of surgery. Auscultation ensured the correct positioning of the endobronchial tube. All surgery was performed in the lateral decubitus position.

Maintenance of anesthesia consisted of a continuous infusion of ketamine, 2 mg·kg^{-1}·hr^{-1}, combined with atracurium, 0.6 mg·kg^{-1}·hr^{-1}, in an infusate of 5% dextrose in water using an IVAC 560 infusion pump. The solution for infusion was made by adding ketamine, 500 mg, and atracurium, 150 mg, to 500 ml of 5% dextrose in water. This infusion was commenced at the time of induction. Subsequent to intubation, mechanical ventilation of the lungs was instituted with a tidal volume of 10 ml/kg at a respiratory rate of 10 breaths/min. Oxygen, 100%, was used throughout surgery. The infusion was maintained at a steady rate throughout the procedure and terminated 15 min before the end of surgery.

Mean arterial pressure, heart rate, and degree of neuromuscular block were documented before induction; after bronchoscopy and tracheal intubation; and 60, 90, and 120 min after induction of anesthesia. Neuromuscular block was assessed by visual determination of the response to a train-of-four stimulus with the number of twitches present after the stimulus recorded. The train-of-four stimulus was delivered via a supramaximal stimulus at 2 Hz applied to the ulnar nerve proximal to the wrist.

Reversal of the neuromuscular block was performed with neostigmine, 5 mg, and glycopyrrolate, 1 mg. Time to recovery from anesthesia and neuromuscular block was documented. The end point for

the former was the ability to elicit an appropriate response to vocal stimulation from the patient and the end point for the latter, the presence of all twitches to a train-of-four stimulus and sustained tetanus at 50 Hz for 2.5 sec applied to the ulnar nerve.

Statistical analysis of the data for MAP and HR was performed using a repeated measures analysis of variance. If the time effect was statistically significant, the data were further analyzed using the Bonferroni multiple comparisons analysis; $P < 0.05$ was considered significant. All patients were interviewed 24 hr postoperatively to ascertain the presence or absence of dreaming and hallucinations and the acceptability of the anesthetic from their point of view.

Results

All patients in our study were men, age 57 ± 8 yr (mean ± SD), weight 72 ± 16 kg, who underwent pulmonary surgery lasting 175 ± 50 min. Onset of anesthesia was rapid in all cases (<45 sec). Three minutes after the administration of atracurium, all patients underwent bronchoscopy followed by laryngoscopy and tracheal intubation. Neuromuscular relaxation was considered satisfactory by both surgeons and anesthesiologist, and no further bolus injections of nondepolarizing neuromuscular blocker were required. No patient regurgitated, vomited, or aspirated, and no patient had recall of intraoperative events.

Mean arterial pressure (MAP) and heart rate (HR) before induction and during anesthesia are summarized in Table 1. The MAP and HR in every patient increased during bronchoscopy. As a group, the mean increase in MAP after bronchoscopy was 12 mm Hg (12%), and was the highest noted during the study. The mean increase in heart rate was 6 beats/min (7%) after bronchoscopy and was again the highest noted in the study.

Repeated measures analysis of variance showed a statistically significant time effect for both MAP ($P < 0.001$) and HR ($P < 0.05$). Further analysis using the Bonferroni multiple comparisons showed MAP after bronchoscopy/tracheal intubation to be statistically

Table 2. Recovery Times and Postoperative Data

	Emergence reactions	Postoperative dreaming	Patient acceptance of anesthesia	Time to Recovery from Anesthesia (min)[a]		
				<15	15–30	>30
All Patients (50)	0%	10 (20%)	100%	26 (56%)	17 (37%)	3 (7%)
Patients age <60 yr (26)	0%	4 (8%)	100%	17 (65%)	9 (37%)	0 (0%)
Patients age >60 yr (24)	0%	6 (12%)	100%	9 (38%)	8 (33%)	3 (13%)

[a]Four patients electively ventilated postoperatively and not assessed.

significantly higher than preoperative and all intraoperative MAP values ($P < 0.01$). No statistically significant differences between preoperative MAP and MAP at 60, 90, and 120 min intraoperatively could be shown. As for HR, the only demonstrated statistically significant difference was between HR after bronchoscopy/tracheal intubation and the preoperative HR level, the former being significantly higher ($P < 0.01$).

The degree of neuromuscular blockade as monitored by the train-of-four stimulus did not vary during the procedure. At the time of bronchoscopy and intubation, seven patients (14%) had total abolition of twitches, 31 patients (62%) had 1–3 twitches, and 12 patients (24%) underwent bronchoscopy with all four twitches present albeit depressed. At the termination of the operative procedure, all but one patient had one or more twitches present in response to train-of-four stimulation. Atracurium was considered adequately reversed, with four twitches and sustained tetanus present within 10 min of the administration of the neostigmine. One patient without a twitch present required 30 min to attain the same endpoint.

The postoperative data are shown in Table 2. No patient experienced emergence delirium. Postoperative dreaming was experienced by ten patients (20%), only one of whom said it was mildly unpleasant. During the postoperative interview, all 50 patients expressed satisfaction with the anesthesia in so far as willingness to undergo the same anesthesia again, should surgery be required.

Time to recovery from anesthesia was variable. Four patients, due to extensive surgery, were electively ventilated postoperatively and thus not assessed for recovery time. Of the remaining 46 patients, 26 (57%), were considered to have appropriate recovery within 15 min of the termination of the procedure, and 43 patients (93%) recovered within 30 min of the end of surgery. The other three patients took longer than 30 min to recover. These three patients were over the age of 60 yr; all patients under age 60 recovered within 30 min of the end of surgery. Patient weight had no effect on recovery times.

No ECG signs of myocardial ischemia were seen at any time in the perioperative period, and no post-

operative or intraoperative complications attributable to the technique were observed. Excessive salivation after airway manipulation, due to the omission of an anticholinergic drug in the preoperative medication, was the only undesirable side effect of the technique. However, this was of aesthetic concern only and posed no clinical problem.

Discussion

The continuous infusion of a ketamine–atracurium mixture is an effective anesthetic technique, producing a clinically constant anesthetic state and in our sample a 100% patient acceptability as defined by postoperative interview.

MAP and HR increased in all patients in response to bronchoscopy and tracheal intubation, and were statistically significantly above preinduction and intraoperative levels. However, the absolute mean increase in MAP was only 12 mm Hg, with a mean increase of 6 beats/min for HR. These are less than increases previously documented in patients given ketamine alone (3,12,13).

These attenuated responses of MAP and HR can be explained by the fact that all the patients were premedicated with droperidol and diazepam. The cardioprotective effects of these two drugs in the presence of ketamine have previously been reported and are related to the inhibition of the increase in plasma catecholamines associated with ketamine (14,15).

After these cardiostimulatory responses associated with airway manipulation, cardiovascular stability was a feature of the technique with little variation and no statistically significant differences in MAP and HR from the preinduction levels. No episodes of intraoperative hypotension were noted.

The major drawback to the use of ketamine as the primary anesthetic has been its association with emergence phenomena and hallucinations. Patients in our study exhibited neither emergence delirium nor hallucinations. However, ten patients admitted to postoperative dreaming, one of whom thought it vaguely unpleasant. This use of droperidol and diazepam to

reduce the incidence of emergence phenomena associated with ketamine confirms a previously reported study by Bovill et al. (16). Consequently, when our preoperative regimen was followed, emergence phenomena were not constraining factors in the use of this technique.

A bolus introductory dose of atracurium, 0.5 mg/kg, followed by an infusion of 0.6 mg·kg^{-1}·hr^{-1}, or 10 μg·kg^{-1}·min^{-1}, provided excellent relaxation for bronchoscopy, tracheal intubation, and surgery. Although only the presence or absence of twitches in response to a train-of-four stimulus was monitored in our study, the degree of twitch suppression remained stable intraoperatively and did not progress with time of infusion of the atracurium. Within the group, considerable variation in the extent of twitch suppression was apparent with 14% of patients exhibiting no response to a train-of-four stimulus. Surgical relaxation, however, was excellent in all patients.

Mean infusion rate for atracurium to obtain a stable neuromuscular block has been variously reported, ranging from 6 μg·kg^{-1}·min^{-1} (10) to 10 μg·kg^{-1}·min^{-1} (17). The infusion rate used in our study, although at the high end of reported rates, is lower than that reported by Payne and Hughes (8) to obtain a stable degree of neuromuscular block using intermittent bolus injections of atracurium. This infusion rate posed no significant problem in regard to termination of the neuromuscular block. Length of surgery did not affect recovery time, even though mean infusion times exceeded 160 min. Discontinuation of the ketamine–atracurium infusion 15 min prior to the completion of surgery allowed complete reversal of the neuromuscular block by neostigmine within 10 min. No episodes of recurrence were observed. The rapid termination of the effects of atracurium is due to its metabolism, whether by Hoffman elimination or, as recently reported, primarily by enzyme-catalyzed hydrolysis (18).

Ketamine hydrochloride is stable in solution and not given to spontaneous degradation. Although atracurium undergoes spontaneous degradation at physiologic pH to yield inactive metabolites, this does not appear to pose any significant problem when atracurium is infused in physiologic infusates. Added to normal saline (pH 5.85) it undergoes less than 1% degradation after 5 hr (19). Our practice of infusing atracurium in dextrose 5% in water (pH 4.4) together with ketamine (pH 3.5–5.5) ensured an even lower rate of spontaneous degradation of atracurium.

In conclusion, the continuous administration by constant rate infusion of a ketamine–atracurium fixed dose mixture produced a steady state of anesthesia and muscle relaxation, a satisfactory operating environment, no significant side effects, and total patient acceptability in patients undergoing pulmonary resection.

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Systemic Responses to Tourniquet Release in Children

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The hemodynamic and metabolic effects of deflation of pneumatic tourniquets were assessed in 15 children, seven of whom had bilateral tourniquets applied. Systemic acidosis from release of lactate and $PaCO_2$ after tourniquet deflation did not cause adverse effects in these healthy children. Larger increases in lactate were seen with longer tourniquet inflation times (>75 min) or with bilateral tourniquets. The greatest decrease in pH was seen with simultaneous deflation of bilateral tourniquets. Heart rate did not change with tourniquet deflation, whereas systolic blood pressure de-creased 8–10 mm Hg with deflation. Blood pressure returned to control values within 5–10 min; no arrhythmias were seen. Recommendations to minimize the systemic metabolic effects after release of tourniquets in children under general anesthesia include the following: 1) attempt to limit tourniquet inflation times to <75 min; 2) use controlled ventilation prior to and after tourniquet deflation to remove the respiratory component of acidosis; 3) check blood gas tensions within 5 min of tourniquet deflation in children with long tourniquet inflation times (>75 min), and where bilateral tourniquets are deflated simultaneously or within 30 min of each other.

Key Words: ANESTHESIA, PEDIATRIC—orthopedic.

Orthopedic surgery of the extremities frequently includes the use of pneumatic tourniquets. Review of the surgical records for 1978–1980 at the Children's Orthopedic Hospital and Medical Center showed that 1628 orthopedic procedures were performed, with pneumatic tourniquets being used in 650 cases, or 40%. Advantages cited for tourniquet use include facilitation of microsurgery by the bloodless surgical field, and decreased blood loss. The time a pneumatic tourniquet may be safely inflated has been studied in adults and in animal models with inflation times of 2–3 hr reported as free of hemodynamic, metabolic, or local compression consequences (1–5).

Venous blood from an extremity made ischemic by a tourniquet shows progressive decreases in pH and PaO_2 and increases in $PaCO_2$ and lactate as ischemic time increases (1). When the tourniquet is deflated, CO_2, lactate, and hydrogen ions enter the general circulation; their effects on blood gases have been studied in adults (2) and in animal models (3), but data from children are limited (6). Because oxygen consumption and metabolic rate are two- to three-fold greater in children than in adults, tourniquet hemostasis may result in greater accumulation of ischemic metabolites or in their appearance after a shorter tourniquet inflation than reported in adults. When these ischemic products enter the circulation with tourniquet deflation, physiologic compensation may not be sufficient in children. Systemic acidosis may cause central nervous system depression, cardiac irritability, decreased sympathomimetic activity, and altered peripheral perfusion, especially if pH values decrease to less than 7.2 (7).

To investigate the hemodynamic and metabolic changes in children in whom surgery included use of tourniquets, we studied the hemodynamic and metabolic responses after release of pneumatic tourniquets in infants and children during orthopedic surgery under general anesthesia. The effects of patient size, method of ventilation (spontaneous breathing vs controlled ventilation), and single vs bilateral extremity tourniquets were investigated.

Methods

Fifteen healthy children (ASA I–II), aged 6 months–15 yr, scheduled for surgical procedures on the extremities that involved the use of pneumatic tourniquets were selected. The study protocol was approved by

Table 1. Patient Description

Patient	Age (yr)	Weight (kg)	Surgery	Anesthesia	Ventilation	Tourniquet site	Tourniquet pressure (torr)	Inflation time (min)
1	3	13.8	McKay release	H, N₂O	C	R thigh	200	46
2	0.5	7.8	Clubfoot release	H	C	R&L thigh	175	35 simult
3	2.1	13.4	Excision of angiolipoma	H, N₂O	S	R thigh	220	41
4	0.5	7.8	Clubfoot repair	H	S	R&L thigh	250	56,50
5	3.7	13.4	Tibial derotation osteotomy	I, F	C	R&L thigh	175	71,48
6	14	84.5	Foot bone biopsy	H, N₂O	S	R thigh	425	94
7	10.9	35.8	Release calcaneonavicular bars	H, N₂O	S	R&L thigh	300	84,81 c̄ overlap
8	14.1	40	Release calcaneonavicular bars	E, N₂O	C→S	R&L thigh	350	62,78
9	14.4	52.8	Bunionectomy	N₂O, F	S	R thigh	350	77
10	0.7	6.8	Vertical talus pinning	H	C	R&L thigh	200	47,52
11	15	61.3	Recurrent ganglion excision	H, N₂O	S	L arm	225	31
12	5.6	23.5	Elbow release	H	S	L arm	250	46
13	8.7	29	Tibial transfers	H, N₂O	C	R&L thigh	300	62,55
14	2	9.6	Tibial osteotomy	H	C	L thigh	150	32
15	3.1	13.4	McKay release	H	S	R thigh	150	57
Mean	6.6							

Abbreviations: H, Halothane; I, Isoflurane; E, Enflurane; F, Fentanyl; R, right; L, left; C, controlled; S, spontaneous; simult, simultaneous.

the hospital's Human Subjects Review Committee, and informed consent was obtained from the parents. Children with known cardiac, pulmonary, or renal disease, and patients with markedly reduced muscle mass were excluded from this study.

Anesthesia was induced with thiamylal administered rectally (25 mg/kg) or intravenously (5 mg/kg); anesthesia was maintained with halothane alone ($n = 6$) or with N₂O ($n = 6$), enflurane with N₂O ($n = 1$), and fentanyl with isoflurane ($n = 1$) or with N₂O ($n = 1$) (Table 1). Monitors included a continuous electrocardiogram, a precordial stethoscope, a temperature probe, oxygen analyzer, and blood pressure. All children had intravenous fluids given at maintenance rates with replacement for fasting periods. After induction of anesthesia, a 22-gauge catheter was placed in the artery of a nonoperative extremity for blood sampling. The extremity undergoing surgery was exsanguinated with an Esmarch bandage and the pneumatic tourniquet inflated to a pressure ≥75 mm Hg higher than the child's awake systolic blood pressure.

Data were obtained serially after induction of anesthesia (control); immediately preceding tourniquet deflation; and 1, 3, 5, and 10 min after deflation of the pneumatic tourniquet. Heart rate and rhythm, blood pressure, temperature, and respiratory rate were recorded at the specified times. Arterial blood was sampled anaerobically for measurements of pH, Pao₂, Paco₂ (IL 813 Instrumentation Laboratories, Lexing-

ton, MA), hematocrit, potassium (flame photometry), and lactate (enzymatic assay) levels on the same time schedule. Samples were stored on ice before being analyzed within 15 min. Base deficits corrected for the child's hematocrit were calculated with a Siggard–Andersen slide rule. When surgery involved both extremities and tourniquets were released sequentially ($n = 6$), data were collected at the time each tourniquet was deflated.

t-Tests for paired data were used to compare control and prerelease values against the later samples. When two tourniquets were used, the second data set was compared to the control values; the second prerelease values were compared to the second postrelease values. To assess whether smaller children had a greater amount of ischemic metabolites appear due to their high metabolic rate, the study parameters were compared between small (<14 kg, $n = 8$) and large (>20 kg, $n = 7$) children by one-way analysis of variance (ANOVA). Effects of type of ventilation (controlled and spontaneous) and comparison of data from children having a single tourniquet with data from the first tourniquet where two were used in series were evaluated by ANOVA. Data are presented as means ± SD. Tourniquet inflation times were correlated with the maximal change in blood chemistries (control minus post release values) by linear regression analysis. Change in pH was calculated as the change in hydrogen ion (H⁺) concentration and converted to pH difference.

Results

Of the 15 children studied, lower extremity tourniquets were used in 13, and upper extremity tourniquets in two. Table 1 summarizes patient age, patient weight, type of surgery, site and inflation pressure of the tourniquet, duration of tourniquet inflation, and the type of anesthesia. Seven children had bilateral lower extremity surgery: in five patients, tourniquets were used serially, that is, the second tourniquet was inflated after the first had been deflated. In one patient (patient 2), tourniquets were inflated and deflated simultaneously; in another patient (patient 7), the second tourniquet was inflated 15 min after the first and released 12 min after the first (see graphic presentation of patterns of tourniquet inflation in Figure 1).
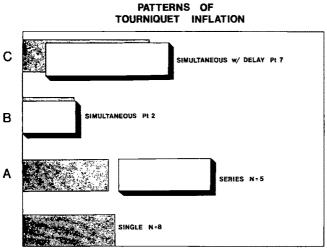
One Tourniquet

Tourniquet times for single (or first) tourniquets ranged from 31 to 94 min (mean 58 min, $n = 14$). Table 2 summarizes the hemodynamic and blood chemistry data from the 14 patients' single or first tourniquet inflation.

Pulse increased with tourniquet inflation and surgical stimulation but did not change with tourniquet deflation. Blood pressure decreased 8 mm Hg transiently with tourniquet release but returned to control values within 5 min. No arrhythmias were seen.

Statistically significant increases in serum lactate, base deficit, and $Paco_2$, and a decrease in pH were seen after tourniquet deflation. Potassium levels increased transiently after tourniquet release for the first 3 min. The lactic acidosis persisted for the entire 10-

min sampling period, but the respiratory component ($Paco_2$) returned to prerelease values by 3 min after tourniquet release.

Comparison of cardiovascular and metabolic data in small (mean 10.8 ± 3 kg) and large children (mean 46.7 ± 20 kg) showed that smaller patients had faster heart rates throughout the sampling period, but blood pressure changes were not statistically different. Changes in metabolic variables (pH, $Paco_2$, base deficit, lactate, potassium) were not associated with patient size.

Children in whom ventilation was controlled ($n = 6$) had higher pH and lower $Paco_2$ values before and after tourniquet release than those breathing spontaneously (Table 3). However, the spontaneously breathing children corrected their pH and $Paco_2$ to prerelease levels more quickly than children managed with controlled ventilation. Base deficit and lactate were not influenced by the mode of ventilation.

Correlation of tourniquet inflation time (min) to the maximal change in metabolic parameters after tourniquet release showed the correlation of tourniquet time to serum lactate was greater ($r = 0.81$ for single or first tourniquet release) than was the correlation of tourniquet time with change in serum pH ($r = 0.39$ for single or first tourniquet). Figures 2 and 3 summarize changes in lactate and pH as a function of tourniquet inflation time.

Two Tourniquets

In six children, two tourniquets were used and deflated serially (Figures 1A, 1C), allowing two sets of data to be collected (Table 4). Analysis of variance showed no difference between the data obtained after release of the first tourniquet in these six children compared to the eight children in whom a single tourniquet was used. Second tourniquets, when used, were inflated 2–26 min (mean 11 min) after the first tourniquet was deflated, and remained inflated for 62 ± 14 min ($n = 6$). The base deficit increased during the time the second tourniquet was inflated, and systemic lactate levels did not decrease. As with first or single tourniquets, pH decreased with deflation of the second tourniquet while $Paco_2$ and lactate levels increased. Systolic blood pressure decreased 10 mm Hg with release of the second tourniquet. In these six children the increase in serum potassium reached statistical significance, but the values all remained within the clinically defined normal range. As with single tourniquets, lactic acidosis was not cleared during the 10-min sampling time, and pH had not returned to control values. A comparison of prerelease to postrelease values for the second tourniquet was made, and

Figure 1. Patterns of tourniquet inflation.

PATTERNS OF
TOURNIQUET INFLATION

C — SIMULTANEOUS w/ DELAY Pt 7

B — SIMULTANEOUS Pt 2

A — SERIES N=5

SINGLE N=8

TOURNIQUET TIME (min)

Table 2. Data from Patients with Single Tourniquets Inflated for 58 ± 19 min ($n = 14$)

Mean ± SD	Control	Pre	Minutes after release			
			1	3	5	10
Heart rate (beats/min)	105 ± 28	114 ± 26[a]	116 ± 21[a]	118 ± 23[a]	115 ± 24[a]	117 ± 21[a]
Blood pressure systolic (mm Hg)	89 ± 12	95 ± 19	87 ± 14[b]	87 ± 14[b]	88 ± 14	90 ± 14
pH	7.38 ± 0.06	7.33 ± 0.07[a]	7.30 ± 0.06[c,d]	7.31 ± 0.07[c]	7.32 ± 0.07[c]	7.32 ± 0.07[c]
$Paco_2$ (mm Hg)	38 ± 7	42 ± 9	45 ± 9[c,d]	42 ± 9	42 ± 8	42 ± 9
Base deficit (mEq/L)	3.2 ± 1.9	4.0 ± 2.0	4.9 ± 2.5[c]	4.8 ± 2.2[c,b]	4.7 ± 2.1[c]	4.6 ± 2.8[c]
Lactate (mol/L)	1.0 ± 0.6	1.1 ± 0.7	1.6 ± 0.8[c,d]	1.7 ± 0.9[c,d]	1.6 ± 0.9[c,d]	1.6 ± 1.0[a,d]
Potassium (mEq/L)	4.0 ± 0.6	4.1 ± 0.3	4.2 ± 0.4[b]	4.2 ± 0.3[b]	4.1 ± 0.4	4.1 ± 0.3

[a] $P < 0.05$ compared to control.
[b] $P < 0.05$ compared to prerelease.
[c] $P < 0.01$ compared to control.
[d] $P < 0.01$ compared to prerelease.

Table 3. Ventilation Mode (Controlled or Spontaneous)

Sampling times	Controlled $n = 6$ pH	Spontaneous $n = 8$ pH	P	Controlled Pco_2	Spontaneous Pco_2	P
Control	7.39	7.37	0.67	36	39	0.59
Pre	7.37	7.29	0.02	37	46	0.05
1[a]	7.33	7.26	0.03	41	48	0.10
3[a]	7.35	7.28	0.03	38	46	0.08
5[a]	7.35	7.29	0.11	39	45	0.16
10[a]	7.35	7.29	0.05	39	45	0.12

[a]Minutes after deflation of tourniquet.
Controlled ventilation: tourniquet time mean = 55.7 min.
Spontaneous ventilation: tourniquet time mean = 60.7 min.

only the decrease in systolic blood pressure and rise in serum lactate reached statistical significance (Table 4, right side). Linear regression showed good correlations for the change in lactate ($r = 0.94$) and pH ($r = 0.85$) as a function of tourniquet duration on deflation of the second tourniquet (Figs. 2, 3).

Patient 2 had bilateral tourniquets deflated simultaneously (Table 4B). His acidosis had both respiratory and metabolic components ($Paco_2$ 27 → 41 mm Hg, base deficit 1.9 → 4.7 mEq/L, and lactate 1.5 → 2.5 mol/L) and was unusual in its progressive development over the 10-min sampling period. This apparently progressive acidosis was primarily due to the increase in $Paco_2$ to the normal range to allow spontaneous ventilation to resume at the end of the procedure. The respiratory alkalosis associated with controlled ventilation had initially compensated for most of the metabolic acidosis seen with tourniquet deflation.

Discussion

Children in this study tolerated tourniquet release with less hemodynamic change than has been reported in adults, where tourniquet deflation resulted in significant decreases in blood pressure (2,8) and in

central venous pressure (8). Unlike Moncorge et al. (6), who studied 11 children and found systolic blood pressure fell and pulse increased by 15 mm Hg and 12 beats/min, respectively, we found a lesser decrease in blood pressure (8–10 mm Hg) with tourniquet deflation and no change in heart rate. No arrhythmias were seen in the children in our study. The children in our study who were all healthy tolerated tourniquet deflation well.

The increase we observed in serum potassium (Table 4) is similar to that found in the previously cited pediatric study (6); potassium levels increased with tourniquet deflation but remained in the normal range. Similar or slightly greater changes in potassium have been reported in adults (2,3,9), ranging from 0.32 to 0.5 mEq/L after tourniquet release.

Wilgis (1) reported a progressive decrease in pH and Po_2, and an increase in Pco_2 in venous blood sampled from a tourniqueted arm in 50 adults undergoing hand surgery. After 1 hr of tourniquet time, venous blood pH reached 7.19, Po_2 20 mm Hg, and Pco_2 62 mm Hg; after 2 hr, pH had decreased to 6.9, Po_2 to 4 mm Hg, and Pco_2 to 104 mm Hg. Time to clear the increase in Pco_2 and hydrogen ions from the general circulation after tourniquet deflation var-

Figure 2. Maximal change in arterial lactate after deflation as a function of tourniquet inflation time (min). □, single or first tourniquet, $y = 0.03x - 0.92$, $r = 0.81$; ■, second tourniquet, $y = 0.07x - 2.7$, $r = 0.94$. (Excludes patient 2, 35 min simultaneous release.)
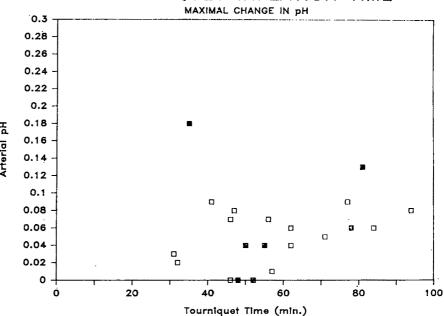
Figure 3. Maximal change in arterial pH after deflation as a function of tourniquet inflation time (min). □, single or first tourniquet, $y = 0.0006x + 0.019$, $r = 0.39$; ■, second tourniquet, $y = 0.003x - 0.123$ $r = 0.85$. (Excludes patient 2, 35 min simultaneous release.)

ied with the duration of tourniquet inflation and, thus, the degree of increase before deflation of the tourniquet; 10 min was sufficient clearance time after 1 hr of arm tourniquet time in Wilgis's study, whereas over 15 min was needed after 2 hr of inflation (1). Resolution of the metabolic acidosis in other adult studies has been reported to take 10–30 min (2,10).

We demonstrated a decrease in arterial pH and increases in $Paco_2$, base deficit, and lactate after re-

lease of pneumatic tourniquets in children under general anesthesia. The transient increase in $Paco_2$ quickly decreased to prerelease levels. In this study neither pH, base deficit, nor lactate had returned to baseline levels within 10 min after tourniquet deflation.

Like adults, children in our study had no adverse effects from the acidosis after tourniquet release. Two patients who had arterial blood gas tensions measured in the recovery area beyond our usual collection

Table 4. Bilateral Lower Extremity Tourniquets

A. Sequential	(n = 6) Control	First tourniquet (62 ± 13 min)					Second tourniquet (62 ± 14 min)				
		Pre	1	3	5	10	Pre	1	3	5	10
Heart rate	109 ± 28	118 ± 31	118 ± 26	119 ± 29	114 ± 26	119 ± 18	122 ± 16	119 ± 10	119 ± 11	118 ± 10	112 ± 13^c
BP systolic	90 ± 9	93 ± 14	87 ± 18	88 ± 17	87 ± 16	91 ± 15	104 ± 17	94 ± 21^c	98 ± 21	91 ± 22^c	94 ± 22^c
pH	7.36 ± 0.04	7.35 ± 0.04	7.30 ± 0.04^a	7.32 ± 0.04^a	7.34 ± 0.06	7.34 ± 0.06	7.33 ± 0.03	7.31 ± 0.07	7.31 ± 0.08	7.34 ± 0.08	7.33 ± 0.09
PaCO$_2$	40 ± 4	40 ± 5	43 ± 5^a	41 ± 6	39 ± 6	39 ± 6	37 ± 5	41 ± 8	40 ± 8	38 ± 7	39 ± 8
Base deficit	3.1 ± 2.2	3.7 ± 2.3	5.1 ± 3.4	5.1 ± 2.9^b	4.8 ± 2.4^a	4.8 ± 3.6	6.2 ± 3.1	6.0 ± 2.4^b	6.0 ± 2.8	5.7 ± 2.9	5.8 ± 3.0
Lactate	1.1 ± 0.4	1.3 ± 0.9	2.0 ± 0.7^b	2.0 ± 0.9^b	2.0 ± 1.1^b	2.0 ± 1.2	2.1 ± 1.3	2.7 ± 1.2^b	3.0 ± 1.4^{b,c}	2.7 ± 1.4^{b,c}	2.8 ± 1.3^b
Potassium	3.8 ± 0.3	4.2 ± 0.2^a	4.2 ± 0.2^a	4.3 ± 0.3^a	4.2 ± 0.4^b	4.1 ± 0.3^b	3.9 ± 0.5	4.3 ± 0.3^a	4.3 ± 0.3^a	4.3 ± 0.3^a	4.2 ± 0.1^a

B. Simultaneous (patient 2, both tourniquets, 35 min)	Control	Pre	1	3	5	10
Heart rate	106	130	133	131	131	130
BP systolic	55	58	59	65	71	73
pH	7.5	7.45	7.44	7.43	7.36	7.32
PaCO$_2$	27	28	29	30	38	41
Base deficit	1.9	3.1	3.8	3.7	3.7	4.7
Lactate	1.5	2.0	2.5	2.5	2.2	1.9
Potassium	3.7	3.8	4.0	4.0	3.9	4.0

All values are mean values ± SD.
^{a} P < 0.01 compared to control.
^{b} P < 0.05 compared to control.
^{c} P < 0.05 compared to second prerelease.

time had corrected their acidosis to baseline levels by 30 min after tourniquet release, similar to data reported in adults (2).

In attempting to predict changes in lactate or pH, an estimate of the increase in serum lactate when tourniquets are released can be made based on the duration of tourniquet inflation. Changes in pH are less predictable. The largest changes in pH were seen in two of our patients (patients 2 and 7) in whom lower extremity tourniquets were in use simultaneously and deflated simultaneously (patient 2, change in pH of 0.18) or were released sequentially 12 min apart (patient 7, change in pH of 0.13).

The changes in pH, $Paco_2$, base deficit, and lactate were similar in smaller and larger children. We were unable to show evidence of more ischemic metabolites due to the presumed higher metabolic rate of small children. However, our sample size was small, so only large differences could have been detected.

Whereas the magnitude of pH change after release of a single tourniquet was the same in patients breathing spontaneously or having controlled ventilation, the children whose anesthetic was managed with controlled ventilation had pH and $Paco_2$ levels closer to awake normal values before and throughout the 10-min sampling period after tourniquet deflation (Table 3). Spontaneously breathing children had elevated $Paco_2$ levels before and after tourniquet deflation.

When sequential bilateral lower extremity tourniquets were used, lactic acid levels did not begin to decrease until the second tourniquet had been deflated for 5 min. This ongoing lactic acidosis during the time the second tourniquet is inflated may represent leakage of nonvolatile acids from the second tourniqueted extremity via bone circulation, as has been previously suggested by Moncorge et al. (6). A monkey model has shown similar changes in mixed venous pH values during tourniquet inflation, although this was not discussed by the author (3). This mechanism may also help to explain the changes seen between control and prerelease values (Tables 2, 4).

In conclusion, release of pneumatic tourniquets in healthy children results in a mild transient decrease in blood pressure lasting less than 10 min. However the degree of blood pressure change in less healthy children has not been assessed. Tourniquet release allows ischemic metabolites to enter the general circulation causing a mixed respiratory and metabolic acidosis. The respiratory element is quickly compensated, but the metabolic acidosis persists for more than 10 min after tourniquet release. The degree of metabolic acidosis increases as ischemic time increases or as the ischemic area increases.

The healthy children in our study experienced no adverse effects from the transient acid load after tourniquet release. However, in attempting to define safe limits, we make the following recommendations:

Because general anesthesia depresses the ventilatory response to acidosis and increasing CO_2 (11), controlled ventilation, at least around the time of tourniquet deflation, can speed elimination of the CO_2 released from the tourniqueted extremity and thus remove the respiratory component of the acidosis more quickly. An induced respiratory alkalosis also can offset the metabolic acidosis until metabolic pathways clear the nonvolatile acids.

The largest change in pH was seen when bilateral lower extremity tourniquets were released simultaneously (Fig. 3). Changes in pH when the second tourniquet was released were the same as with first tourniquets unless both deflations occurred close together (patients 2 and 7). When bilateral tourniquets were used sequentially, lactate levels, which increased with the first tourniquet release, remained elevated during the inflation time of the second tourniquet. This lactic acidosis did not begin to be cleared until the second tourniquet had been deflated. When lower extremity tourniquets are inflated for longer than 75 min, when bilateral lower extremity tourniquets are deflated simultaneously or within 30 min of each other, or if tourniquets are used in children with associated medical problems (renal disease, chronic pulmonary disease) that would make them less able to compensate for an acid load, arterial blood gas analysis should be performed within the first 5 min after tourniquet deflation to identify those who require treatment for their acidosis.

Our correlation studies found that larger changes in lactate (>1.5 mol/L) occurred with single tourniquet times longer than 75–80 min or with second tourniquets used for over 60 min. Attempts to minimize single tourniquet duration to less than 75 min and second tourniquets to under 60 min appear indicated.

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Intrathecal Morphine for Post-Thoracotomy Pain

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We wished to investigate possible differences in the duration of postoperative analgesia and the incidence of respiratory depression after the intrathecal injection in the lumbar area of 10 µg/kg morphine in hypobaric and hyperbaric solution for relief of post-thoracotomy pain. Twenty-nine patients received morphine plus dextrose (hyperbaric) and 21 received morphine in preservative-free normal saline. The duration of analgesia was longer with the morphine in the normal saline group than in the hyperbaric group (P < 0.04). One patient developed delayed respiratory depression. Our data support the use of morphine in normal saline mixtures for greater duration of analgesia after thoracic operations.

Key Words: ANESTHETIC TECHNIQUES, SPINAL—morphine. ANALGESICS—Morphine. PAIN—postthoracotomy.

Patients undergoing thoracotomy experience significant postoperative pain accompanied by respiratory impairment (1,2). Recent reports suggest that epidural narcotics provide significantly better postoperative analgesia and pulmonary function than systemically administered morphine (3,4). Additionally, intrathecal morphine has been employed for postoperative analgesia with good success with a wide range of doses from 0.5 mg in patients after inguinal herniorrhaphy (5) to 20 mg after laparotomy or thoracotomy (6).

Our practice has been to administer narcotics epidurally for relief of post-thoracotomy pain. However, we wished to investigate the duration of pain relief and the incidence of side effects using relatively low dosages of morphine given intrathecally for the management of post-thoracotomy pain. In addition, rostral spread of morphine has been implicated in causing late respiratory depression due to morphine. To examine this aspect, we assigned patients to one of two groups to determine whether rostral spread is affected by the baricity of the morphine solutions injected intrathecally. One group of patients received morphine in normal saline, 1.0 mg/ml, while the other group of patients received morphine as above mixed with an equal volume of 10% dextrose so the injected

solution had a final concentration of 5% dextrose (hyperbaric).

Methods

We administered intrathecal morphine in doses ranging from 0.5 mg to 1.2 mg (mean 0.79 mg) to 50 consecutive post-thoractomy patients who had undergone 31 pulmonary, 11 mediastinal, and eight thoracoabdominal procedures. Table 1 shows the distribution in each group. These patients did not have contraindication to lumbar puncture and consented to the procedure. The age of the patients ranged from 17 to 81 yr (mean 57 yr) with 31 men and 19 women. All patients received inhalation anesthetics with volatile agents supplemented with a mean of 7.5 mg of intravenous morphine or a mean of 375 µg fentanyl intraoperatively. Upon arrival in the recovery room and after extubation of the trachea, the patients were placed in the lateral recumbent position with the operative site up for injection.

Two anesthesiologists were responsible for the anesthetics given to these patients, including the intrathecal morphine. One anesthesiologist administered intrathecal morphine diluted only in normal saline (1 mg/ml) to his patients, whereas the other anesthesiologist administered the intrathecal morphine (1 mg/ml) mixed with an equal volume of 10% dextrose.

Intravenous fentanyl was provided in the postanesthesia recovery room to those patients requesting medication while awaiting onset of analgesia from intrathecal injection. Lumbar puncture at L2–3 or L3–4

Table 1. Distribution of Patients
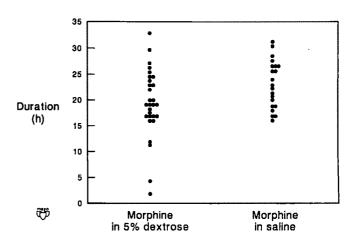
Procedure	Group 1 (morphine in normal saline)	Group 2 (morphine and dextrose)
Lobectomy or Wedge Resection of Lung	16	9
Decortication of Pleura	2	1
Pneumonectomy	2	1
Esophageal Reflux Correction	3	4
Excision of Mediastinal Tumor	3	1
Thoracoabdominal Esophagogastrectomy	3	4
Thoracoabdominal Nephrectomy	—	1
	n = 29	n = 21

Figure 1. Distribution of duration of analgesia in individuals receiving morphine in saline or morphine in 5% dextrose.

was done via a midline approach in all but a few cases in which a paramedian approach was used after unsuccessful midline attempts. A 22-gauge spinal needle was used in all patients above 50 yr of age. At age 50 or below, a 25-gauge spinal needle was used. Intrathecal morphine was then given based on the patient's weight in a dose of 10.0 μg/kg with small decreases in this amount in the presence of severe preexisting pulmonary disease. After injection, patients were positioned supine with the head elevated 15–30°. Patients were told to ask for additional parenteral or oral medication when their pain returned. They were also told that some discomfort during coughing and deep breathing was to be expected but that otherwise they should be comfortable. No additional intrathecal injections were given. All patients were in an intensive care unit for at least 16 hr after discharge from the postanesthesia recovery room.

Charts were examined for time, dosage, and frequency of additional parenteral or oral analgesics. Duration of analgesia was defined as the time from administration of intrathecal morphine to the time additional parenteral or oral analgesic was given. Also, charts were checked for indications of respiratory depression (decreased rate and associated changes in arterial blood gas tensions), as well as for administration of narcotic antagonists.

Results

Thirty-one patients underwent pulmonary procedures including pneumonectomy, lobectomy, and wedge resection of lung. Eleven patients had procedures involving mediastinal structures, including seven procedures for esophageal reflux, three excisions of mediastinal tumors, and one segmental tracheal resection. The remaining eight patients had thoracoabdominal incisions for Ivor–Lewis esophageal resections (5), esophagogastrectomy (3), and one thoracoabdominal nephrectomy. Twenty-nine patients

received intrathecal morphine in 5% dextrose, and 21 received morphine in normal saline (Table 1). During these procedures, ribs were spread, and no ribs were resected in any of the patients.

While awaiting the onset of analgesia from the intrathecal injection, eight patients (three in the morphine saline group and five in the morphine 5% dextrose group) were given intravenous fentanyl in doses ranging from 12.5 μg to 50 μg (mean 35 μg) for postoperative pain. None received intravenous injection more than 30 min after intrathecal narcotic. The shortest duration of analgesia in these eight patients was 18 hr, and none suffered delayed respiratory depression.

Only four patients out of 50 (8%) requested additional analgesics prior to 16 hr after injection of intrathecal morphine sulfate. Eight of the patients (16%) required no other parenteral narcotics during their entire hospital stay.

One patient (2%) had postoperative respiratory depression with a $PaCO_2$ of 59 mm Hg, necessitating administration of narcotic antagonist 6.5 hr after administration of intrathecal morphine. This patient had received morphine without dextrose. One patient had pruritis, requiring administration of diphenhydramine.

The duration of action of intrathecal morphine was significantly longer when morphine in saline was injected as opposed to morphine in 5% dextrose ($P < 0.04$) (Fig. 1), even though the dosage and age range of the groups were not significantly different (Table 2).

There was a small correlation ($r = 0.35$) between duration of action and age, indicating longer duration as age increased ($P < 0.05$) (Fig. 2). Follow up questioning on the ward failed to find postspinal headache reported by any of our patients.

Table 2. Age, Dosage, and Duration of Action with Intrathecal Morphine

	Hypobaric (n = 21)	Hyperbaric (n = 29)	Difference
Age (yr)	56.60 ± 15.70	57.60 ± 17.00	P = 0.83
Dosage (mg)	0.80 ± 0.16	0.78 ± 0.17	P = 0.67
Duration (hr)	22.90 ± 4.40	19.30 ± 6.50	P = 0.04

Age of patients (mean ± SD); dosage (mean ± SD); duration of analgesia (mean ± SD) for hypobaric and hyperbaric groups. Compared using 2-sample t-test for age and dosage and with Wilcoxon's Rank-Sum Test for duration.

Discussion

Since the description of administration of intrathecal morphine by Wang et al. in 1979 (7), there have been several applications of this technique for both chronic (8) and acute pain (9–11). Most of the descriptions of the technique for acute pain involve abdominal, orthopedic, or open heart surgical procedures. Though the literature is replete with descriptions of epidural narcotics for post-thoracotomy pain (3, 11, 12) reports of the use of the intrathecal route for this purpose are limited.

Postoperative respiratory abnormality after abdominal or thoracic surgery has a restrictive pattern with decreased vital capacity and functional residual capacity (13). The goal of limiting the extent of the pulmonary function abnormality can be at least partially accomplished with effective pain relief without respiratory depression. Indeed, Shulman et al. have shown that respiratory function is significantly better with epidural than with intravenous morphine given for post-thoracotomy pain (4). Though excellent postoperative analgesia has been reported with intrathecal doses from 2 mg to 15 mg without sequelae (6), excellent pain relief has been achieved with lesser dosages as well (7). The safest course, therefore, would seem to be giving the minimum effective dose hoping to minimize the possibility of respiratory depression. In our study, we showed that excellent analgesia can be achieved with doses of 1.2 mg and less. That 16% of the patients required no further parenteral narcotics speaks to the quality of pain relief. Further, only four of our 50 patients (8%) requested additional parenteral analgesics prior to 16 hr after the administration of intrathecal morphine. This is not different (P = 0.73) than the seven of 129 (5.4%) who requested additional analgesics while receiving epidural morphine for post-thoracotomy pain in a similar group of patients at our institution reported by Fromme et al. (14).

The duration of analgesia was significantly longer in the patients receiving morphine without dextrose intrathecally. To our knowledge, this has not been
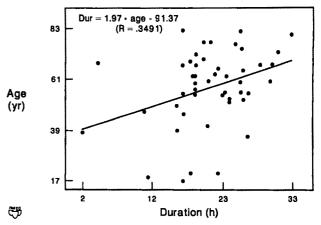

Dur = 1.97 · age - 91.37 (R = .3491)

Figure 2. Duration of analgesia as a function of age.

reported previously. This is consistent with a previous study of hyperbaric and hypobaric local anesthetics in man (15). We can speculate on how the addition of dextrose alters pharmacokinetics of intrathecal morphine. Perhaps the dextrose slows the spread of the morphine molecules in the cerebral spinal fluid, allowing relatively more molecules to bind to lumbrosacral opioid receptors (nearer to the site of injection) and relatively fewer molecules reach the thoracic segments to bind there. Upon further redistribution and vascular absorption of these bound molecules, the thoracic area has a loss of analgesia before the lumbrosacral area. However, we are aware of animal studies showing that there are no signficant differences in numbers of dermatomes blocked by local anesthetics in hypobaric, hyperbaric, or isobaric solutions (16). The duration of analgesia was longer in the older patients; this is consistent with the findings of others (9).

Comparing duration of the single intrathecal injection to continuous (reinjected) epidural technique, the duration of analgesia with the epidural technique is obviously longer due to repeated injections of morphine. Indeed, the continuous epidural technique may be an advantage to those patients requiring more than one day in the intensive care unit with the thoracostomy tube in place. However, intrathecal administration has the advantage of being a simple technique and not requiring placement of an indwelling catheter with its inherent risks.

Delayed respiratory depression is the most feared side effect of intraspinal narcotics. The rostral spread of morphine in the subarachnoid space to the cisterns and then to the pons is thought to be responsible for the diminished respiratory drive (18). Samii et al. suggested morphine in hyperbaric solutions may diminish rostral spread (6). In our study, the patient with

respiratory depression had not been given a hyperbaric mixture of morphine. However, because only one patient had respiratory depression, a statistical comparison is not meaningful. Administration of naloxone, 0.4 mg, in our patient did not reverse the analgesia, and indeed, the patient received the first parenteral narcotic at 26 hr after the intrathecal injection. The incidence of respiratory depression in this group of patients was no different than in a similar study using epidural morphine in our institution (14).

Pruritis has been reported in incidences of 1% (19) to 28% (20) in postoperative patients given intraspinal morphine. However, there appears to be a spectrum of intensity of pruritis. Indeed, some of our patients admitted to some pruritis on careful questioning postoperatively, but it was troublesome in only one patient. This patient received diphenydramine intravenously, and the itching abated.

Many of our patients had indwelling urinary catheters placed preoperatively. Therefore, we did not feel that a comment on the incidence of urinary retention would be meaningful to this study.

We conclude that intrathecal morphine can provide effective analgesia in post-thoracotomy patients. The duration of analgesia provided by a single intrathecal injection is less than that provided with multiple injections through an epidural catheter. The incidence of side effects in the patients given intrathecal morphine or morphine in 5% dextrose did not allow for meaningful comparison. Analgesia was signficantly longer in those given morphine in saline solution compared to morphine in 5% dextrose mixture. This finding has not been described previously and needs to be further examined. Because of the delayed respiratory depression that may occur, we recommend patients given intrathecal narcotics be monitored in an intensive care unit for at least 16 hr after injection of the drug. Further studies are necessary to quantitate the difference in pulmonary function between patients receiving intrathecal morphine and those given traditional parenteral narcotics, and the impact of the route of morphine administration on postoperative course before routine use of intrathecal morphine is recommended.

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Atracurium, Vecuronium, and Intraocular Pressure in Humans

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SCHNEIDER MJ, STIRT JA, FINHOLT DA. Atracurium, vecuronium, and intraocular pressure in man. Anesth Analg 1986;65:877-82.

We studied 60 nonophthalmologic patients, allocated to six treatment groups, to assess the effects of atracurium and vecuronium on intraocular pressure (IOP). All patients had IOP measured while awake, using pneumotonometry. In group 1, anesthesia was induced with thiopental, 5 mg/kg, and maintained with N_2O, 70% in O_2, using controlled mask ventilation, for 5 min. These patients then received atracurium, 0.5 mg/kg. After 5 additional minutes of ventilation, the trachea was intubated. From 1 min after thiopental administration until 1 min after intubation, IOP was recorded every minute. Patients in groups 2, 3, and 4 were treated identically to those in group 1, except the muscle relaxant given was atracurium, 1.0 mg/kg, vecuronium,

0.1 mg/kg, or vecuronium, 0.2 mg/kg, respectively. Patients in groups 5 and 6 underwent rapid sequence induction with thiopental, 5 mg/kg, and atracurium, 1.0 mg/kg, or vecuronium, 0.2 mg/kg, respectively. IOP was measured 1 min later, followed by intubation and IOP measurements for the next 3 min. Intraocular pressure decreased significantly in groups 1, 2, 4, and 6 after thiopental and remained stable in all groups during ventilation with N_2O. Neither atracurium nor vecuronium affected IOP, nor was there any correlation between IOP and degree of neuromuscular blockade. However, IOP increased significantly after intubation in all six groups. We conclude that atracurium or vecuronium alone has no adverse effects on IOP.

Key Words: EYE—intraocular pressure. NEURO-MUSCULAR RELAXANTS—atracurium, vecuronium.

The relationship between intraocular pressure (IOP) and muscle relaxants is of interest to anesthesiologists for both academic and clinical reasons. Succinylcholine has been demonstrated to cause dramatic increases in IOP that may result in extrusion of vitreous humor in patients with an open globe (1–4). On the other hand, a recent study demonstrated no loss of ocular contents after succinylcholine in 63 patients undergoing emergency open eye surgery (5).

Studies of commonly used nondepolarizing agents have shown they are not associated with increases in IOP as seen with succinylcholine (6–10), but few of these investigations have succeeded in eliminating the confounding effects on IOP of premedication, anesthetics, tracheal intubation, alterations in Pa_{CO_2}, hemodynamic changes, and surgical stimulation. To our knowledge, studies isolating the effects on IOP of the nondepolarizing relaxants atracurium or vecuronium in humans have not been performed. In this paper we show the effects of these new drugs on IOP in a controlled, prospective study. In addition, we report on the effects of these agents on IOP during

rapid sequence induction, the clinical situation to which this issue is most relevant.

Methods

This study was approved by the institution's Human Investigation Committee, and written informed consent was obtained from each patient. Sixty unpremedicated adult patients between 18 and 60 years of age undergoing orthopedic, gynecologic, or general surgical procedures were randomly allocated into six groups of ten each. Forty patients (Part 1) had non-rapid sequence induction of anesthesia. Twenty patients (Part 2) underwent rapid sequence induction. Patients with glaucoma were excluded.

Part 1—Nonrapid Sequence Induction

Group 1. Each of ten patients received one drop of 0.5% tetracaine ophthalmic solution in the eye, after which IOP was measured and recorded by pneumotonometry (Digilab Model 30RT, Precision Electronics). After placement of electrocardiogram (ECG) leads, an automated blood pressure (BP) cuff (Dinamap® Model 845, Critikon, Inc.) and preoxygenation, intravenous (IV) sodium thiopental, 5 mg/kg, was administered over 10 sec. Controlled mask ventilation with N_2O, 70% in O_2, was begun once the eyelid reflex was lost.
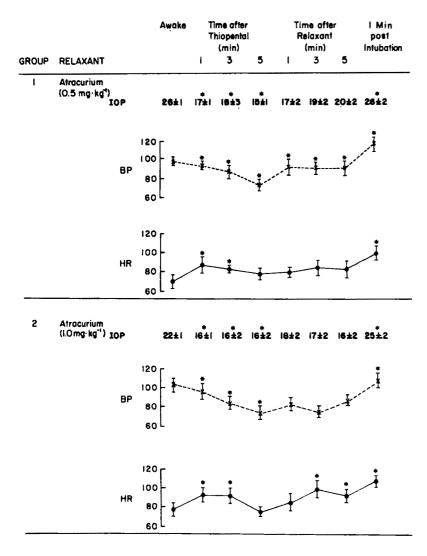
End-tidal CO_2 (ET_{CO_2}) was monitored (Hewlett-

Figure 1. Intraocular pressure (IOP, mm Hg, mean ± SEM), mean arterial blood pressure (BP, mm Hg, broken line), and heart rate (HR, beats/min, solid line) in nonrapid sequence induction patients receiving atracurium, 0.5 or 1.0 mg/kg (groups 1 and 2, Part 1 of study). Values 1, 3, and 5 min after thiopental were compared with awake control values; values 1, 3, and 5 min after relaxant were compared with the value 5 min after thiopental; 1 min postintubation values were compared with values 5 min after relaxant.

$*P < 0.05$.

Packard model 47310-A) and maintained between 35 and 40 mm Hg during the study period. Neuromuscular function was monitored with a force-displacement transducer (Grass Model FT-10) and recorder (Gould 220 series) measuring adductor pollicis twitch tension in response to supramaximal stimuli of 0.15-msec duration at 0.15 Hz delivered to the ulnar nerve via 25-gauge needles placed subcutaneously.

Intraocular pressure; systolic, diastolic and mean BP; heart rate (HR); and $ETCO_2$ were recorded every minute for up to 5 min after thiopental. Patients then received atracurium, 0.5 mg/kg IV, over 30 sec. Mask ventilation was continued, and IOP was recorded every minute for 5 min. Intraocular pressure was also recorded at 25, 50, 75, and 100% neuromuscular block. The trachea was intubated, and IOP was again measured 1 min later after intubation.

Group 2. Patients were treated identically to those in group 1, except that atracurium, 1.0 mg/kg, was given instead of atracurium, 0.5 mg/kg.

Group 3. Patients were treated identically to those in group 1, except that vecuronium 0.1 mg·kg^{-1} was used instead of atracurium 0.5 mg·kg^{-1}.

Group 4. Patients were treated identically to those in group 1, except that vecuronium, 0.2 mg/kg, was used instead of atracurium, 0.5 mg/kg.

Occasionally, patient movement precluded the full 5-min period of measurement after thiopental administration. In such patients, atracurium or vecuronium was administered 3–4 min after thiopental administration.

Part 2—Rapid Sequence Induction

Group 5. After awake measurement of IOP as in group 1, an ECG and Dinamap® blood pressure cuff were placed, and patients were preoxygenated for 3 min. Thiopental, 5 mg/kg IV, was then given over 10 sec, immediately followed by atracurium, 1.0 mg/kg
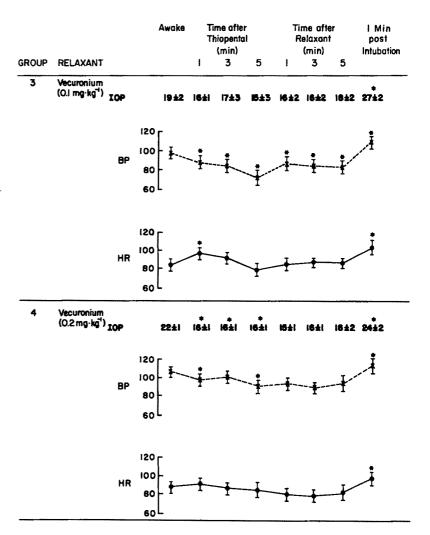
Figure 2. Intraocular pressure (IOP, mm Hg, mean ± SEM), mean arterial blood pressure (BP, mm Hg, broken line), and heart rate (HR, beats/min, solid line) in nonrapid sequence induction patients receiving vecuronium, 0.1 or 0.2 mg/kg (groups 3 and 4, Part 1 of study). Values 1, 3, and 5 min after thiopental were compared with awake control values; values 1, 3, and 5 min after relaxant were compared with the value 5 min after thiopental; 1 min postintubation values were compared with values 5 min after relaxant.
*$P < 0.05$.

IV, over 10 sec. Cricoid pressure was applied and after 1 min, IOP, systolic and diastolic BP, and HR were recorded, and intubation was performed. For the 3 min after intubation, IOP, BP, and HR were recorded every minute while controlled ventilation with N_2O, 70% in O_2, maintained $ETCO_2$ between 35 and 40 mm Hg.

Group 6. Patients were treated identically to those in group 5, except that vecuronium, 0.2 mg/kg IV, was given instead of atracurium, 1 mg/kg.

Statistical Methods

Baseline group characteristics prior to the study were compared using one-way analysis of variance (ANOVA). In addition, changes in IOP or HR after intubation were compared between groups using ANOVA. If ANOVA showed significant differences between groups, multiple t-tests were performed us-

ing Bonferroni's and Sheffe's methods of correction for multiple comparisons.

Student's paired t-test was used to compare IOP, BP, and HR before and 1, 3, and 5 min after thiopental; values 1, 3, and 5 min after muscle relaxant with values immediately prior to relaxant administration; and values before and after intubation.

To analyze trends within each group during ventilation with N_2O and after muscle relaxants, we used both one-way analysis of variance and regression analysis. Analysis of correlation coefficients between IOP, BP, and HR within each group was performed to identify relationships between these variables. $P < 0.05$ was considered statistically significant.

Results

There were no significant differences between groups in age or weight. Mean (± SEM) ages of patients in groups 1–6 were 35 ± 4, 41 ± 6, 34 ± 3, 48 ± 4,

39 ± 2, and 46 ± 6 years, respectively. Mean (± SEM) weights were 72 ± 5, 71 ± 5, 77 ± 4, 81 ± 6, 69 ± 7, and 73 ± 7 kg, respectively. Awake BP or HR was not significantly different between groups. Awake IOP (mean ± SEM) in groups 3 and 5 (19 ± 2 and 19 ± 1 mm Hg, respectively) was significantly lower than in groups 1, 2, 4, and 6 (26 ± 1, 22 ± 1, 22 ± 1, and 23 ± 1 mm Hg, respectively).

Part 1—Nonrapid Sequence Induction

Figures 1 and 2 show recorded variables in groups 1, 2, 3, and 4 throughout the study. Intraocular pressure decreased significantly below awake values after thiopental in groups 1, 2, and 4. There were no significant changes in IOP during the 5-min periods before or after atracurium or vecuronium. With intubation, all groups showed significant increases in IOP. Intraocular pressure increases after intubation were not statistically different between groups. The onset of neuromuscular block >90% required 4 min in groups 1 and 3, and 3 min in groups 2 and 4. There was no significant correlation between IOP and the degree of neuromuscular block.

Cardiovascular changes paralleled changes in IOP in all four groups. Blood pressure decreased significantly after thiopental and during ventilation with N_2O and O_2, remained stable after muscle relaxants, and increased after intubation. Heart rate increased significantly after thiopental in groups 1, 2, and 3, remained relatively stable before and after muscle relaxants, and showed a further significant increase after intubation. Heart rate increases after intubation were not statistically different among groups.

Part 2—Rapid Sequence Induction

Figure 3 shows results obtained in patients receiving rapid sequence induction. Intraocular pressure decreased significantly after thiopental and atracurium in group 5, but not after thiopental and vecuronium in group 6. One minute after intubation, IOP increased significantly in both groups, from 17 ± 2 to 24 ± 2 mm Hg (mean ± SEM) in groups 5 and from 17 ± 1 to 27 ± 2 mm Hg in group 6. Intraocular pressure remained stable during the three postintubation measurements.

Blood pressure, which decreased significantly only after thiopental and vecuronium, increased and remained elevated after intubation in both groups. Heart rate increased only after thiopental and atracurium but increased significantly and remained elevated in both groups after intubation. Correlation of IOP with BP and HR showed a significant positive correlation
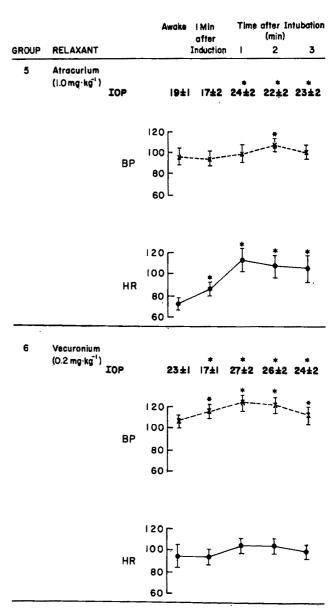

Figure 3. Intraocular pressure (IOP, mm Hg, mean ± SEM), mean arterial blood pressure (BP, mm Hg, broken line), and heart rate (HR, beats/min, solid line) in rapid sequence induction patients (groups 5 and 6, Part 2 of study). Values 1 min after induction were compared with awake control values; values 1, 2, and 3 min after intubation were compared with value 1 min after induction.
*P < 0.05.

between IOP and BP for patients receiving atracurium or vecuronium.

Intubating conditions were excellent in 18 of the 20 patients in groups 5 and 6. In the other two patients (group 6, vecuronium, 0.2 mg/kg), the vocal cords were adducted at the beginning of laryngoscopy, but opened to permit intubation within 30 sec. Time from thiopental/atracurium administration until intubation was completed in group 5 was 85 ± 4 sec (mean ± SEM), with a range of 71–105 sec. Time from thiopen-

tal/vecuronium administration until intubation in group 6 was 89 ± 4 sec (mean ± SEM), with a range of 70–111 sec.

Discussion

Since the original observations that succinylcholine is associated with substantial and, in the case of patients with open globes, disastrous increases in IOP (1–4), there have been many clinical studies on the effects of muscle relaxants on IOP (6–10). Measurement of the effects of muscle relaxants on IOP is fraught with difficulty, due both to problems in reliably measuring IOP and to the many confounding factors influencing IOP.

The Schiotz method of tonometry has generally been abandoned as a research tool owing to the changes in IOP produced by multiple measurements with this technique (11). Applanation tonometry produces less fluid displacement but is best done in the seated position, and is thus not ideal for IOP measurements during general anesthesia (12). The Freon-driven pneumotonometer is reliable and accurate (13–16). Pneumotonometry is also the only one of the three commonly employed methods of IOP measurement designed to produce a printed record of IOP as it is determined. Interobserver variation in measurement is still a potential problem, and careful technique in applying the tonometer is needed to avoid artifactual increases in IOP.

Studying the effect of muscle relaxants on IOP requires controlling the effects of all other drugs. Giving a paralyzing dose of muscle relaxant to an awake patient and measuring IOP is not feasible. Assuming that patients must receive general anesthesia for such a study, it should be recognized that most general anesthetics alter IOP, usually causing a decrease from awake values (12,17,18). In addition, tracheal intubation, patient position, $Paco_2$, surgical stimulation, changes in cardiovascular dynamics, intracranial pressure alterations, changes in venous drainage from the head, coughing, and airway obstruction are all capable of affecting IOP (12). For these reasons we elected to use only N_2O, 70% in O_2, as an anesthetic after thiopental induction, and measured IOP for up to 5 min after thiopental until IOP was stable, before administering muscle relaxant.

Several patients moved during light levels of thiopental/N_2O anesthesia. Removing data obtained from these patients from our analyses did not significantly affect the results. Thus we have included them in our reporting. Selecting only those patients who could be ventilated with a mask for 5 min prior to paralysis would have selected a nonrandom group of patients, perhaps affecting our results in an unpredictable fashion. We also kept patients supine, unpremedicated, free of tracheal and surgical stimulation, and with constant alveolar ventilation, restrictions not employed in most previous studies (6–10,19–22). Potent inhalation agents or narcotics, commonly used in other studies (6,7,9,22,23), might have abolished changes in IOP that could have been due to atracurium or vecuronium.

We have demonstrated a method for isolating, insofar as possible, the effect of a given muscle relaxant on IOP from other influences while a patient is receiving general anesthesia. Intraocular pressure was stable after the initial thiopental-induced decrease, and before and after atracurium and vecuronium in groups 1, 2, 3, and 4. After intubation, there was a consistent increase in IOP, as noted in previous studies employing various nondepolarizing agents (8,9,19–21).

In addition to determining the effects of atracurium and vecuronium on IOP, we have also employed these drugs in the clinical situation in which IOP is of most concern, i.e., during a rapid sequence induction as occurs in a patient who needs emergency ocular surgery but has an open globe. In this setting, we have shown that changes in IOP 1 min after intubation during rapid sequence induction are not statistically different from those occurring 1 min after intubation in a nonrapid induction sequence.

It should be noted that a recent study (5) demonstrated the apparent safety of succinylcholine use in patients about to undergo emergency open-eye surgery. Whether this retrospective review (5) of the charts of approximately 45% of patients presenting for such surgery in 1982 at one facility is representative of results to be expected elsewhere must remain an open question. In addition, one must decide whether the simple absence of extrusion of global contents represents an optimal result, or whether the inevitable elevation of IOP after succinylcholine administration might have other as yet uncharacterized but deleterious effects on ocular integrity in patients with damaged globes.

Increases in BP, which correlated well with IOP, were seen after intubation with both atracurium and vecuronium. This implies that either of these new drugs can be used in the patient with an "open eye" requiring rapid sequence intubation, but that the major burden of the anesthesiologist will be to minimize the cardiovascular stress of intubation as reflected by increases in BP and HR. It would seem appropriate to use IV narcotics or lidocaine, or possibly a larger thiopental dose prior to laryngoscopy in such pa-

tients, to minimize the adverse effects of intubation on IOP.

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Special Article

Selection of Patients for Implantable Intraspinal Narcotic Delivery Systems

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The use of intraspinal narcotics represents a major advance in the management of pain of malignant origin. For patients whose pain is uncontrolled by narcotic analgesics and adjunctive drugs, a trial of intraspinal narcotics is warranted. If the patient perceives adequate pain relief, an implantable intraspinal narcotic delivery system (INDS) may be indicated.

The use of epidural narcotics to treat cancer pain was first described by Behar et al. in 1979 (1). More recently, a variety of implantable INDSs have been described (Table 1) for long-term intraspinal narotic administration (2–8). Most authors agree on the need for a preimplantation trial of intraspinal narcotics, but no mention is made of any patient selection process. We wish to describe the selection process that we have used prior to implanting one particular INDS, type III INDS, in 35 patients, and to review the factors that must be evaluated when considering a patient for an INDS. As with any pain management procedure, appropriate patient selection is crucial to ensure a successful outcome.

The first factor to consider when selecting a patient for implantation of an INDS is whether intraspinal narcotics adequately relieve the patient's pain. Not all pain is relieved by intraspinal narcotic (9–11). For this reason, an implantable INDS should *never* be implanted without first verifying the ability of intraspinal narcotics to relieve the patient's pain on at least two occasions. Failure to do so could subject the patient to implantation of a delivery system that fails to achieve the desired results—namely pain relief.

Table 2 outlines a suggested protocol for the preimplantation trial for intraspinal narcotics. The expected result of the preimplantation trial of intraspinal narcotics is adequate pain relief as perceived by the patient. This relief should be of appropriate duration for the narcotic analgesic injected (12). Other variables that should be quantified include the level of activity, the use of narcotics by other routes, and the amount and quality of sleep.

Side effects secondary to the intraspinal narcotics including pruritus, urinary retention, and respiratory depression must be noted. These side effects must be acceptable to the patient before implantation can be considered. Any inconsistency in the expected versus the observed results should alert the pain management specialist to delay implantation of the delivery system and consider the patient's ability to assess pain relief.

The ability of the patient to accurately assess the adequacy of pain relief is essential to avoid the implantation of an intraspinal narcotic delivery system that will be deemed useless. Impairment of this ability may be either physiologic or behavioral in origin.

Physiologic abnormalities that may impair the patient's ability to assess the adequacy of pain relief are listed in Table 3. Many of these abnormalities are reversible, and every attempt should be made to correct them before a trial of intraspinal narcotics is undertaken. It should be remembered that the central nervous system (CNS) symptoms caused by these abnormalities may be incorrectly interpreted as uncontrolled pain by the patient and pain management specialist alike.

Behavioral factors that may affect the patient's ability to assess the adequacy of pain relief (Table 4) are often difficult to identify. They may coexist with phys-

Table 1. Intraspinal Narcotic Delivery Systems

Type I   Percutaneous epidural or subarachnoid catheter (2)
Type II Percutaneous epidural or subarachnoid catheter with
         subcutaneous tunneling (3)
Type III Totally implanted epidural or subarachnoid catheter
         with subcutaneous injection site (4,5)
Type IV Totally implanted epidural or subarachnoid catheter
         with implanted reservoir bag and manual pump (3)
Type V   Totally implanted epidural or subarachnoid catheter
         with implanted infusion pump (6-8)

iologic factors, but care must be taken not to attribute inadequate pain relief solely to behavioral factors until all other reasons have been explored.

A patient who received adequate pain relief during the preimplantation trial may be a candidate for implantation of an INDS. The adequacy of patient motivation, patient support system, concurrent therapy, systemic infection, life expectancy, and the cost of intraspinal narcotic must also, however, all be evaluated before referring a patient for implantation.

An implantable INDS requires a baseline level of commitment not only from the patient but from the support system as well. The person or persons designated as the patient's support system must be acceptable to the patient in the role of care provider. If this is not the case, problems may arise. This person must be available night and day to care for and inject medication into the delivery system should the patient be unable to do so. It should be remembered that the patient who injects narcotics into his own delivery system initially may be unable to do so later in the course of his disease. If the support system is unable or unwilling to care for the delivery system, the continuous infusion pump may be a better option; however, someone must be available to bring the patient to the pain center to have the pump refilled. It is important also to consider the possibility that there may be family members who will divert the patient's drugs for illicit purposes.

Before proceeding with implantation of an INDS, a review of concurrent primary therapy and its potential to relieve the pain is indicated. Long-term administration of intraspinal narcotics should be reserved for patients in whom primary modes of tumor eradication (surgery, chemotherapy, and radiation therapy) did not relieve pain. We palliate the patient's pain with single epidural injections of narcotics as needed while observing the effect of the primary therapy. If a patient continues to require intraspinal narcotics in spite of adequate primary therapy, then implantation of an INDS is indicated.

The cancer patient may have quantitative and qualitative problems with clotting that may be further

Table 2. Protocol for Preimplantation Trials of
Intraspinal Narcotics

1. Explain the procedure, expected goals, and potential side effects to the patient and his family.
2. Select an appropriate narcotic for intraspinal administration.
3. Determine the appropriate dosage and volume of diluent expected to relieve the pain.
4. Administer the intraspinal narcotic and diluent via the intended route of delivery, i.e., epidural or subarachnoid.
5. Quantify on a flow sheet the duration of pain relief, level of activity, amount of sleep, and need for additional narcotic analgesics.
6. Quantify the side effects of intraspinal narcotics.
7. Repeat the trial to quantify the results.
8. Observe 24 hr after intraspinal narcotics and requantify variables listed in 5. before proceeding with implantable INDS.

Table 3. Common Physiologic Abnormalities that May
Interfere with the Patient's Ability to Assess Pain Relief

Metabolic encephalopathy
  Hypercalcemia
  Hyponatremia
  Hypoxemia
  Hypercarbia
  Azotemia
  Hepatic encephalopathy
  Paraneoplastic syndrome
Drug-induced organic brain syndrome
  Narcotic
  Minor tranquilizers
  Barbiturates
  Phenothiazine reactions
  Cimetidine
Structural brain disease
  Metastatic tumor
  Increased intracranial pressure
  Preexisting structural abnormality
    Cerebral infarction
    Cerebral hemorrhage
    Abscess
Preexisting neurodegenerative disorders
  Alzheimer's disease

compromised by chemotherapy and radiation therapy (13,14). In our experience, this has not presented any practical problems; however, in the cancer patient receiving systemic anticoagulants the risk of epidural hematoma is a possibility (15). In these patients, the risk:benefit ratio of the anticoagulants must be weighed carefully.

In the immunocompromised cancer patient, ongoing infection is not uncommon. We have never seen a spinal infection secondary to an INDS. Zenz et al. reported on 40 patients in whom percutaneous epidural catheters were left indwelling for up to 118 days without spinal infection (2). Epidural abscess formation as well as spondylitis have, on the other hand,

Table 4. Common Behavioral Abnormalities that May Interfere with the Cancer Patient's Ability to Assess Cancer Pain

Preexisting psychiatric illness
Preexisting chemical dependence
Use of pain as a controlling device
Use of pain to obtain more medication to alter the sensorium
Use of pain as an attention-seeking device
Patient's refusal to accept the person designated as care-giver
Patient's use of pain to punish certain care-givers within the support system

been reported in some cases when percutaneous catheters were advanced into the epidural space without subcutaneous tunneling and left in place for as little as 6 days (16–18). It appears that for long-term usage, an INDS that is totally implanted or subcutaneously tunneled is superior to a percutaneous indwelling epidural catheter. Common sense dictates against placing an indwelling foreign body in a septic patient.

A realistic appraisal of life expectancy is necessary to determine the appropriateness of an invasive and relatively expensive procedure for pain relief. For patients with a limited life expectancy, it may be more reasonable to simply percutaneously place an epidural or subarachnoid catheter with subcutaneous tunneling.

When evaluating the costs of an INDS, it is necessary to consider costs of both the system and the drugs to be administered through it. The hardware for an INDS can run up to $5000 for a totally implantable infusion pump. This is exclusive of professional fees and hospital charges. The cost of a prefilled syringe of 7 mg standard morphine sulfate diluted in preservative-free saline is currently $4.20 in the Kansas City area. A prefilled syringe of 7 mg of commercially available morphine in saline is approximately $12.20. This does not include the cost of sterile equipment, including antiseptic solutions, sterile prep swabs, gauze, etc. Some patients simply cannot afford the daily expense. Cost must be considered before implanting a delivery system that will not be used.

In summary, implantable narcotic delivery systems are useful adjuncts to cancer pain management. Proper patient selection is crucial if optimal results are to be achieved. By examining the variable factors that may affect the outcome, patient selection can be improved. Preimplantation trials of intraspinal narcotics are a mandatory and integral part of the selection process.

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Review Article

Esophageal Intubation:
A Review of Detection Techniques

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Although the first reported oral intubation of the human trachea occurred in 1878 (1), the procedure did not become standard practice until many years later. It is now a routinely performed procedure, one of the first techniques to be encountered by the anesthesia trainee. It is performed by individuals of different backgrounds and levels of training in the operating suite, emergency room, intensive care unit, hospital ward, and in the field.

However, the frequency of tracheal intubation in modern anesthetic practice belies its importance, and the ability to accurately evaluate proper endotracheal tube position is crucial. A review of various anesthetic-related morbidity and mortality statistics (2–8) indicates that unrecognized esophageal intubation remains a problem, even among anesthesia personnel, a medical population specifically trained in such a procedure.

An analysis of anesthetic accidents reported to the Medical Defence Union of the United Kingdom from 1970 to 1978 revealed that nearly half the cases resulting in death or cerebral damage were due to faulty technique (2). The technique most often identified as the source of mishap was tracheal intubation, with inadvertent esophageal tube placement the usual problem (2). Another review of anesthesia-related medical liability claims in the United Kingdom from 1977 to 1982 listed esophageal intubation as a "main cause" of accidents leading to death or neurologic

damage, with the largest claims resulting from such mishaps (6). An investigation of anesthesia mortality in Australia revealed 69% of the deaths to be related to airway management, with esophageal intubation once again identified as a contributing factor (7).

In the US, unrecognized esophageal intubation was identified as a significant problem in a study in one institution of cardiac arrests attributed solely to anesthesia (8). There were 27 cardiac arrests among 163,240 anesthetics over a 15-yr period. Of these 27 cardiac arrests, four were due to unrecognized esophageal intubation. In reviewing malpractice claims brought against Washington State anesthesiologists from 1971 to 1982, researchers found that esophageal intubation figured prominently among complications resulting in cardiac arrest, brain damage, and death (9). Of 192 claims, seven were brought for unrecognized esophageal intubation. In several of these cases, chest auscultation was recorded on the anesthetic record. The authors of this report emphasized that "even a conscientious, careful anesthesiologist may be unable to differentiate tracheal from esophageal intubation by the commonly employed methods" (9).

In a survey sponsored by the American Society of Anesthesiologists' Committee on Professional Liability, one of us (RJW) analyzed 29 anesthesia-related insurance claims in which unrecognized esophageal intubation was the cause of injury. In 18 of the 29 cases, auscultation of the chest was documented in the anesthetic record.

It is not only the frequency of misadventure but the potentially catastrophic consequences that underline the importance of being able to recognize and correct an esophageal intubation. We will review the reliability of commonly prescribed methods of assessing tube position after attempted endotracheal intubation, and then offer a solution to the problem.

Commonly Prescribed Methods

Direct Visualization

Direct visualization of the vocal cords and watching as the tube passes into the trachea is considered by many the "gold standard" of correct tube placement and remains one of the most reliable signs. Unfortunately, this is impossible to achieve in certain patients, even in the most experienced hands, due to a multitude of factors. Even after visualization of the cords and tube placement, the tube may be inadvertently withdrawn from the trachea prior to or during securing of the tube, or with positioning of the patient in the lateral or prone position. Additionally, radiographic studies have shown that flexion or extension of the neck can change tube position as much as 5 cm, resulting in inadvertent extubation (10,11).

Chest Movement

Another commonly relied upon measure is observation of symmetric bilateral movements of the chest wall during ventilation. However, conditions in which ventilation is more than usually dependent on diaphragmatic movement make assessment of proper tube position by chest expansion difficult. In the patient with large breasts, obesity, a barrel chest from lung disease, or other conditions resulting in a rigid chest wall, chest movement can be difficult to evaluate.

More important, movement of the chest wall simulating ventilation of the lungs can be seen with an esophageally positioned tube. Confirmation of this phenomenon exists in numerous anecdotal reports of expansile upper thoracic movements noted with an ultimately diagnosed esophageal intubation (12–15). Pollard and Junius (12) demonstrated chest movements "identical to those seen when the lungs are inflated" with ventilation through an endotracheal tube intentionally inserted into the esophagus of a recently deceased man prior to the onset of rigor mortis. Progressive dissection from the epigastrium cephalad showed the chest movements were caused by "the flat esophagus distending into a firm tube which lifted the heart and upper mediastinal structures forward, thus elevating the sternum and ribs" (12).

Mechanisms other than balloon-like esophageal expansion have been proposed. Distension of the stomach with air can cause outward movement of the epigastrium, mimicking downward diaphragmatic movement and outward movement of the lower chest. Escape of gas from the stomach up the esophagus with release of bag compression would allow the diaphragm to fall and the lower chest to move inward (12,13).

Breath Sounds

The presence of bilateral breath sounds upon apical and/or midaxillary auscultation of the lungs would seem to be strong reassurance of proper tube position, based on experience, common sense, and some studies (16). However, the literature documents numerous cases (12–15,17) with experienced clinicians where apparently "normal" breath sounds were present with esophageal ventilation. Air passing through the esophagus has been noted to resemble coarse or tubular breath sounds (17,18). Howells and Riethmuller (13) suggest that the combination of "esophageal wall oscillation with gas movement and acoustic filtering" can produce wheezes similar to adventitial sounds arising from the lungs.

In addition, with mechanical or hand ventilation, gas flows tend to be faster, tidal volumes larger, and distribution different from what is observed with spontaneous respiration. Breath sounds are more predominantly bronchial and may differ in quality, depending on whether the chest is auscultated over the midline or laterally (12). This may explain why sounds produced by air movement through an esophageal tube may be mistakenly identified as breath sounds.

Epigastric Auscultation and Observation

Auscultation of the epigastrium to determine the absence of air movement in the stomach is recommended by some as a maneuver to be done before thoracic auscultation itself (17). Yet vesicular breath sounds can be transmitted to the epigastric area of tracheally intubated thinner or smaller individuals, such that differentiation between gastric air movement and breath sounds may be difficult.

Along with auscultation of the epigastrium comes observation of the abdomen for gastric distension. With esophageal reflux of air, the abdomen does not necessarily progressively distend with intermittent gastric inflation (12,15). Linko et al. (16) point out that gradual gastric filling can be difficult to distinguish from normal abdominal movements. The presence of gastric distension might also be attributable solely to mask ventilation prior to attempted intubation.

Presence of Exhaled Tidal Volumes

An additional point of emphasis is the possibility of measurable tidal volumes during the triad of spontaneous respiratory efforts with the esophagus intubated and the trachea obstructed. Robinson (19) documented tidal volumes up to 180 ml and peak flows greater than 50 L/min under these circumstances. With prior consent obtained, patients were tracheally in-

tubated and allowed to breathe spontaneously. The esophagus was then intubated and the tracheal tube deliberately occluded. With spontaneous respiratory efforts, high intrapleural pressures were generated and transmitted to the esophagus. The degree of reservoir bag movement depends on the strength and coordination of the ventilatory effort and on the fresh gas flow rate, but patients may be able to move the bag and mimic normal respiration in such a setting.

Reservoir Bag Compliance

Another practice commonly adhered to is noting the characteristic feel of the reservoir bag associated with normal lung compliance during inspiration and the presence of expiratory refilling of the bag during hand ventilation. However, compliance varies widely from one person to another and within the same individual at different times. Repeated filling and emptying of the stomach with esophageal ventilation, leading to inflation and deflation of the breathing bag, can also be mistaken for pulmonary ventilation (12,13,16,20).

Endotracheal Tube Cuff Maneuvers

With the cuff deflated, the higher pitched sound of air escaping around a tracheal tube, compared to the more guttural sound of leakage around an esophageal tube, has been used as a distinguishing feature. However, with the cuff of an esophageal tube located near the level of the cricoid cartilage, the distinction in air sound may no longer exist (12).

Palpation of the endotracheal tube cuff in the neck to verify position has also been reported to fail (20), perhaps because the easily distensible esophagus simply balloons outward with an inflated cuff inside it.

Air Escape

A less commonly performed procedure involves pressing sharply on the sternum while listening over the tube opening to detect "a characteristic feel and sound of expelled air" (12). This is unreliable because of inability to distinguish between air expelled from a tracheal tube from: a) that passing through or around an esophageal tube; b) esophageal air present from mask ventilation prior to intubation; or c) air expelled from the nose.

Tube Condensation

Condensation of water vapor in the tube lumen, although less likely with esophageal intubation, can occur and hence is not a reliable sign. Conversely,

the absence of condensation normally seen with a tube positioned in the trachea would be reason to look for further proof of correct tube position.

Gastric Contents

The presence of gastric contents in the tube (21) and/ or the "death rattle" sometimes produced by the entrance of gastric fluid into the tube lumen (15) have led to the diagnosis of esophageal intubation. This may be difficult to distinguish from sounds produced by aspirated fluid or excessive secretions in an endotracheal tube.

Chest Radiography

Chest radiography to verify proper tube position is clearly too time-consuming and expensive, yet not a fail-safe even when performed. A prolonged esophageal intubation occurred during which a radiologist, pulmonary fellow, and additional residents failed to note malposition of the endotracheal tube border outside the tracheobronchial column in not one but two radiographs (21).

Video Stethoscope

Huang et al. (22) demonstrated the possibility of intraoperative use of a "video stethoscope" to ascertain lung ventilation. The device involves a small plastic electrocardiographic electrode casing fitted with a microphone and placed on skin overlying each hemithorax. By displaying the sound from each microphone on an oscilloscope screen in an X-Y format, distinct visual patterns were produced by esophageal, right main stem bronchial, and normal tracheal intubation. The device "conveniently and reliably provided continuous assurance of bilateral ventilation" in a patient population of 25 (22). This device, however, is relatively awkward and time-consuming to use.
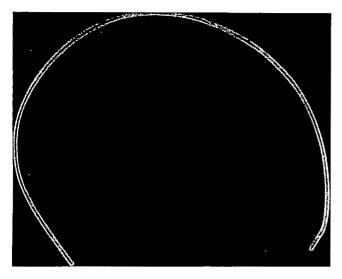
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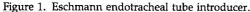
Visualization of tracheal rings and carina by fiberoptic bronchoscopy is a reliable method of verifying tracheal tube placement. However, the instrument is relatively expensive, prone to breakage, and the method is unwieldy for routine use.
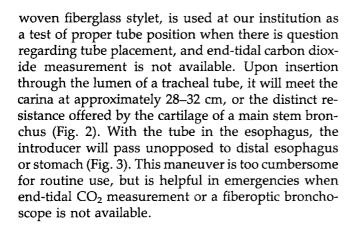
Eschmann Endotracheal Tube Introducer

The Eschmann endotracheal tube introducer (Downs Surgical, Decatur, GA) (Fig. 1), a narrow 60-cm-long

Figure 1. Eschmann endotracheal tube introducer.

Figure 2. Introducer in trachea.

woven fiberglass stylet, is used at our institution as a test of proper tube position when there is question regarding tube placement, and end-tidal carbon dioxide measurement is not available. Upon insertion through the lumen of a tracheal tube, it will meet the carina at approximately 28–32 cm, or the distinct resistance offered by the cartilage of a main stem bronchus (Fig. 2). With the tube in the esophagus, the introducer will pass unopposed to distal esophagus or stomach (Fig. 3). This maneuver is too cumbersome for routine use, but is helpful in emergencies when end-tidal CO_2 measurement or a fiberoptic bronchoscope is not available.

Pulse Oximetry

Pulse oximetry, although useful in many situations, may be a late indicator of esophageal intubation for several reasons. Several authors (12,16,21) have noted normal functioning of a ventilator when connected to an esophageal tube. With the vocal cords relaxed, mechanical (or manual) ventilation into the esophagus can cause alveolar gas exchange. In 18 of the 20 patients studied by Linko et al. (16), after deliberate intubation of both esophagus and trachea, ventilation into the esophagus also caused ventilation of the lungs, as evidenced by carbon dioxide recordings obtained from the open endotracheal tube. The mechanism postulated was a "cyclic external compression of the lungs by the distending stomach and esophagus" (16). Therefore, in the clinical situation where the vocal cords have been relaxed (abducted) by the administration of neuromuscular blocking agents, esophageal ventilation can cause ventilation of the lungs, albeit with room air. This is significant because ventilation

of the lungs with room air will considerably slow the onset of hemoglobin desaturation and cyanosis after esophageal intubation. This can delay recognition of tube misplacement until surgery is in progress or distractions such as record keeping are taking place. Another factor that significantly slows the onset of hypoxia after esophageal tube misplacement is preoxygenation prior to intubation (12,17,23,24). Detection of hemoglobin desaturation with pulse oximetry may therefore provide a relatively late sign of tube malposition.

End-Tidal Carbon Dioxide Measurement

Perhaps the most reliable and simple determination of proper tube placement involves capnometry, the measurement of carbon dioxide concentration during the respiratory cycle, and/or capnography, the display of this concentration in a wave form on a screen or paper graph. The reliability of carbon dioxide monitoring is based on the assumption that CO_2 can be reliably detected in patients with an intact pulmonary circulation whose trachea is intubated, whereas no CO_2 is present in gases exiting from an esophageal tube.

Easily identifiable CO_2 curves are obtained with ventilation through the trachea (16,25,26). Carbon dioxide can be detected initially with esophageal intubation when expired CO_2 has been forced into stomach during prior mask ventilation. However, the end-tidal CO_2 is low in such cases, the wave pattern irregular, and CO_2 levels rapidly diminish with repeated ventilation, making it easy to distinguish between intratracheal and intraesophageal tracings (16).

There are a number of commercially available de-
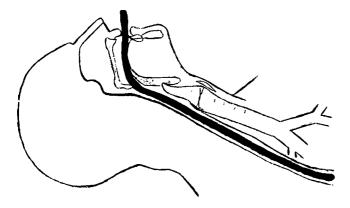
Figure 3. Introducer in esophagus.

Table 1. Evaluations of Methods of Assessing Tube Position

Documented incidents of failure	Reference
End-tidal carbon dioxide measurement	None
Direct cord visualization	None
Equal bilateral breath sounds	12–15, 17
Symmetric bilateral hemithorax elevation	12–16
Epigastric auscultation and observation	12, 15–17
Reservoir bag compliance and refilling	12, 13, 16, 20
Presence of tidal volumes with respiratory effort	19
Normal ventilator function	12, 16, 21
Cuff palpation in neck	20
Quality of air sound escaping around tube	12
Chest radiography	21

vices for measuring carbon dioxide, such as apnea monitors, of which there are approximately 30 different models, ranging in price from $1100 to $10,250 (27). Among the devices employed at our institution is the portable Tri-Med system (Biochem International, Inc., Waukesha, WI), used in the operating suites, with the intensive care unit ventilators, and available during emergency intubations throughout the hospital and in the field (28). It produces a quantitative readout of minute respiratory rate based on qualitative measurement of carbon dioxide. There are also some 16 different quantitative carbon dioxide analyzers on the market, from $2995 to $7885 (29), which produce a quantitative readout of end-tidal carbon dioxide levels.

Finally, the mass spectrometer can produce a continous CO_2 wave form, as well as a digital value. Such a setup allows for rapid diagnosis of accidental intraoperative disconnection of the breathing circuit between ventilator and endotracheal tube, an event identified by Cooper et al. as the most frequent "preventable anesthetic mishap" (30). Intraoperative tube obstruction from secretions or kinking also can be diagnosed. Even inadvertent movement of the tube tip from the trachea into the retropharynx can be detected by the distinctly different end-tidal CO_2 wave forms produced (26). Others (31) have emphasized the noninvasiveness of such monitoring, and have stressed that no other parameter can so readily evaluate the status of both the ventilatory and metabolic systems. Duberman and Bendixen (32) state that "the capnometer is the best device for warning of an undetected esophageal intubation." An assessment of human and technology-related anesthesia errors by a nonprofit biomedical engineering research firm notes that, combined with blood pressure and heart rate measurement, carbon dioxide monitoring "comes

closest to being a fail-safe monitor for most problems that can cause anoxia and death" (33).

In summary, tracheal intubation is a maneuver today so routinely performed in anesthesia that it no longer receives the respect it deserves and the attention it demands. Undiagnosed esophageal intubation continues to figure prominently in anesthesia-related morbidity and mortality. Most of the commonly utilized methods of assessing tube position have been documented to fail under certain circumstances (Table 1). End-tidal carbon dioxide measurement is at present perhaps the most reliable means under all circumstances of determining proper tube position and should be employed routinely whenever possible.

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Clinical Reports

The Magnitude of Hypoxemia in Elderly Patients with Fractures of the Femoral Neck

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Because elderly patients with fractures of the femoral neck have been said to be hypoxemic (1), we undertook a study to determine whether differences in arterial oxygen tension (PaO_2) levels in elderly patients with femoral neck fractures and in a comparable group of elderly patients scheduled for abdominal or urologic procedures were statistically significant, and if so, whether the differences were related to a decrease in platelet counts normally associated with femoral neck fractures in geriatric patients.

Materials and Methods

Thirty patients, 20 with fractures of the femoral neck and ten scheduled for abdominal or urologic surgery, were divided into three groups. The 20 patients with femoral neck fractures scheduled for internal fixation within 2–11 days of the fracture were divided into two groups: ten were given 250,000 U/day of the proteinase inhibitor aprotinin (Trasylol[R], Bayer Pharmaceutical, FRG) intravenously for 3 days after admission (aprotinin group); the other ten were not administered aprotinin (fracture group). None of the three groups received blood transfusions before surgery. The control group consisted of ten patients scheduled for abdominal or urologic operations. The mean age ± SEM of patients in the fracture group, in the aprotinin group, and in the control group were 77 ± 3, 77 ± 4, and 73 ± 2 yr, respectively (Table 1).

Preoperative chest x-rays were similar in the three groups and were normal for the ages of the patients. There was no electrocardiographic evidence of myocardial ischemia, although incomplete right bundle branch block was found in two patients in the fracture group.

All patients received atropine 30 min before blood sampling as their only preoperative medication. In the fracture group, epidural anesthesia was employed for six patients; spinal anesthesia for three patients; and general anesthesia with nitrous oxide, oxygen, and enflurane in one patient. In the control group, epidural anesthesia was used for one patient; spinal anesthesia for three patients; general anesthesia with neuroleptanesthesia for four patients; and general anesthesia with halothane, nitrous oxide, and oxygen for two patients. Before induction of anesthesia, arterial blood samples were taken without local anesthesia from the femoral artery of all patients resting in a supine position while breathing room air. The arterial blood samples were placed in an ice bath prior to measurement of PO_2, PCO_2, and pH on a blood gas analyzer (Model IL-513, Instrumentation Laboratory, MA) within 15 min of sampling. Blood gas measurements and calibration of this instrument were done by the same person throughout the period of this study.

Blood gas tensions, red blood cell (RBC) count, platelet count, hemoglobin (Hb), and hematocrit (Ht) were measured at the same time. Before blood sampling, blood pressure, heart rate, and body temperature were also measured. None of the patients appeared unduly apprehensive. Predicted PaO_2 levels, based on the age of each patient, were calculated using the formula of Raine and Bishop (2).

$$PaO_2 = 103.7 - 0.24 \times (age) \text{ mm Hg}$$

Table 1. Blood Gas Tensions in the Three Groups

Case	Age(yr)			PaO₂(mm Hg)			PaCO₂(mm Hg)			pH			Base excess (mEq/L)		
	C	F	A	C	F	A	C	F	A	C	F	A	C	F	A
1	66	64	76	93(88)	75(88)	83(86)	39	37	38	7.38	7.50	7.39	−2	6	−1
2	68	60	66	96(87)	84(89)	76(88)	31	41	30	7.42	7.42	7.25	−3	3	−12
3	66	85	66	90(88)	80(83)	74(85)	33	27	39	7.43	7.46	7.38	−2	−2	−1
4	77	91	85	91(85)	69(82)	74(84)	38	35	39	7.45	7.48	7.41	3	1	1
5	81	75	75	88(84)	65(86)	75(86)	40	41	36	7.38	7.41	7.55	−1	2	11
6	75	90	90	76(86)	51(82)	70(82)	37	35	26	7.39	7.38	7.49	−1	−3	−1
7	71	74	80	83(87)	81(86)	80(85)	43	35	38	7.41	7.45	7.44	2	1	2
8	72	78	78	89(86)	83(85)	75(85)	35	39	31	7.52	7.42	7.46	6	1	0
9	78	74	80	81(85)	77(86)	68(85)	34	37	35	7.50	7.43	7.44	4	1	1
10	74	78	60	85(86)	64(85)	80(90)	35	34	41	7.44	7.48	7.46	1	3	5
Mean	73	77	77	87(86)	73(85)[a,b]	76(86)[a,b]	36	36	35	7.43	7.44	7.43	0.7	1.2	0.5
SEM	2	3	3	2(0)	3(1)	2(1)	1	3	2	0.01	0.01	0.03	0.9	0.8	2.0

Figures in parentheses are predicted levels. C, control group; F, fracture group without aprotinin; A, fracture group treated with aprotinin.
[a]Significantly different from measured PaO₂.
[b]Significantly different from control PaO₂.

All values were expressed as means ± SEM. The paired Student's t-test was used for statistical analysis, and $P < 0.05$ was considered statistically significant.

Results

None of the 20 patients with femoral neck fractures developed clinically recognizable shock. All, however, had PaO₂ values below predicted levels, and one of the 20 had a hypoxemia (PaO₂ of 51 mm Hg) severe enough to be associated with metabolic acidosis. Tables 1 and 2 show the PaO₂, RBC, Ht, Hb, and platelet counts in the three groups. The PaO₂ values in the fracture and aprotinin groups (73 ± 3 and 76 ± 2 mm Hg, respectively) were significantly lower than those in the control group (87 ± 2 mm Hg), but all values were in the low normal range. The predicted PaO₂ in the fracture and in the aprotinin groups (85 ± 1 and 86 ± 1 mm Hg, respectively) was significantly higher than the measured PaO₂, but this was not the case in the control group (86 mm Hg).

None of the three groups developed CO₂ retention. There were no significant differences in PaCO₂ and pH in the three groups. In the fracture group, whether the patients were treated with aprotinin or not, the RBC, Ht, Hb, and PaO₂ values were significantly lower than in control patients.

The platelet counts in patients with fractures who did not receive aprotinin were significantly lower than in the control group, but platelet counts in patients with fractures who were given aprotinin did not differ significantly from those in the control group. Aprotinin prevented reduction in platelets in the blood in patients with fracture of the femoral neck. There was no significant difference between the fracture group

and the aprotinin group in the operative days after trauma. No correlation existed between the number of days after the trauma and PaO₂ values. No unusual reactions or side effects were noted in the ten patients treated with aprotinin.

Discussion

In this study we observed reductions in PaO₂, platelet counts, and hemoglobin concentration in blood in elderly patients with fractures of the femoral neck. These changes in patients with fractures were almost similar to those found by previous authors (1,3–7).

Our results suggest that a reduction in PaO₂ in patients with fractures is related to the bone fractures, not advanced age. Wilson et al. (7) have shown that the patients with the lowest platelet counts tended to have the lowest PaO₂ after uncomplicated fractures. Their results indicated that platelets may play an important role in the development of hypoxemia in patients with fractures. Haideman et al. (8) demonstrated with radioactive methods that platelets aggregate in the blood and are trapped in the lung after soft tissue injuries in dogs but erythrocyte levels in the various organs remain essentially unchanged, and that aprotinin counteracted the platelet aggregation and trapping. The concomitant reduction in platelet counts with hypoxemia in patients with fractures indicates that hypoxemia may be due to a mechanical obstruction of the blood vessels, including aggregated platelets (9).

As Hass et al. (9) demonstrated, aprotinin is able to reduce platelet activation in patients during total hip replacement surgery. From these observations we designed this study to determine whether aggrega-

Table 2. Hematologic Findings in the Three Groups

Case	RBC (× 10⁶/mm³)			Hb (g/dl)			Ht (%)			Platelet (× 10³/mm)			Days	
	C	F	A	C	F	A	C	F	A	C	F	A	F	A
1	4.59	4.46	3.78	15	14	12	44	40	34	244	233	275	7	8
2	3.60	3.65	3.06	10	12	10	32	36	27	—	145	103	10	10
3	4.05	3.95	3.09	12	11	9	37	32	30	—	122	178	2	6
4	4.36	3.42	3.51	14	11	11	41	34	32	231	—	—	2	11
5	3.79	3.81	4.31	13	12	13	39	34	39	313	150	—	6	8
6	3.15	2.15	3.11	9	7	10	28	20	32	311	173	225	11	3
7	4.79	3.38	3.89	15	11	12	43	32	36	162	197	215	6	10
8	4.95	3.60	3.84	15	12	11	44	36	34	343	199	197	2	5
9	3.57	3.52	3.18	12	10	10	35	29	28	329	228	207	3	5
10	5.03	3.94	4.81	16	12	14	46	34	40	238	—	294	5	6
Mean	4.19	3.59[a]	3.66[a]	13	11[a]	11[a]	39	33[a]	33[a]	271	181[a]	212	5	7
SEM	0.21	0.19	0.16	1	1	1	2	2	2	22	14	21	1	0.5

C, F, and A as in Table 1.
RBC, red blood cell counts; Hb, hemoglobin levels; Ht, hematocrit; Days, operative days after trauma.
[a]Significantly different from control group.

tion of platelets might contribute to hypoxemia in patients with fractures. Aprotinin is a proteinase inhibitor with a stabilizing effect on platelets in vitro (10) and with inhibition of aggregation of platelets and serotonin release (11). In this study, aprotinin is able to prevent a reduction on platelet counts, but not reduction of either PaO₂ or Hb concentration. These results suggest that a reduction in platelet counts may be due to aggregation in blood but that this does not contribute to reduction in PaO₂. The reduction in Hb concentration may be due to hemodilution resulting from extravascular fluid shifts to compensate for large blood losses occurring in fractured extremities (12). We conclude that the cause of reduction in PaO₂ in patients with fractures of the femoral neck involves a number of factors, not the least of which is fat embolism (13–15). Proteinase inhibition with aprotinin prevents the decrease in platelets but does not decrease the reduction of PaO₂ associated with fractures of the femoral neck.

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Epidural Blood Patch for Postdural Puncture Headache: It's Never Too Late

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Postdural puncture headache is an unfortunate complication of spinal anesthesia, lumbar puncture, and myelography. Many of these headaches resolve spontaneously during the week after the procedure (1); if not, therapeutic intervention may be necessary. Many therapeutic maneuvers have been used with mixed success. The most reliable is the epidural blood patch, which since its original description (2) has become widely used in the treatment of postdural puncture headache (3–5).

Most reports describe the use of an epidural blood patch within days after the onset of postdural puncture headache, and there are a few case reports describing its use for headache of up to 8 months' duration (6–8). There are none beyond this time.

The following case report describes a postdural puncture headache lasting nineteen months and its ultimate successful treatment using an autologous epidural blood patch.

Case Report

A 45-yr-old, obese female was evaluated at the Pain Clinic in September 1985 with a 19-month history of persistent headache. This headache began after a myelogram performed in January 1984 as part of an investigation for recurrent back pain with radiculopathy initiated by a lifting injury. The day after the myelogram, the patient awoke with a throbbing frontooccipital headache, exacerbated by coughing. The headache was still present two days later when the patient was discharged from the hospital. During the next 3 months, the patient experienced persistent photophobia, requiring her to wear dark sunglasses

whenever she was in daylight; intermittent dizziness, which prevented her from driving; together with nausea and occasional vomiting. She was hospitalized twice during this period for exacerbation of the existing symptoms and was treated on both occasions with intramuscular meperidine and promethazine.

She was initially referred to the pain clinic 3 months after the onset of the headache for evaluation of her condition. Her symptoms at this time were as described above; neurologic examination confirmed the presence of photophobia but was otherwise normal. A diagnosis of postdural puncture headache was made, and the patient was offered an epidural blood patch, which she declined. The patient was lost to follow-up for the next 16 months, when she was again referred to the pain clinic. During these 16 months she was hospitalized four times for her ongoing symptoms, which essentially remained unchanged. Treatment during hospitalization again consisted of bed rest with intramuscular meperidine and promethazine. Diagnostic procedures performed during this time were negative, including a computed tomography CT scan. When seen on this occasion, the patient's presenting symptom remained that of frontooccipital headache, only minimally relieved by lying supine. She continued to require sunglasses during daylight hours because of photophobia and had not driven because of dizziness. She also continued to experience occasional nausea but had no further vomiting. Medications included Tolacen (pentazocine, 25 mg, and acetominaphen, 650 mg), two tablets four times a day; methocarbamol, two 500-mg tablets 4 times a day; temazepam, 15 mg at bedtime; pentazocine, 50 mg every 4 hr as necessary for pain; thyroxine, 0.3 mg daily; and furosemide, 40 mg daily. Neurologic examination again revealed photophobia but was otherwise normal. Diagnosis of postdural puncture headache was reached once again, and the patient was offered an epidural blood patch, to which she agreed. This was performed through the same

interspace as the previous myelogram (L3–4). The epidural space was identified using a 17-gauge Tuohy needle; 10 ml of the patient's venous blood, drawn under aseptic conditions, was injected into the epidural space. The patient remained supine for 30 min. After this time she remarked that her headache had gone, and this remained so on assuming an upright position. The patient was contacted at 1 week and 6 weeks after the procedure at which time she had remained symptom free. She no longer requires sunglasses during the day and has resumed driving.

Discussion

This report demonstrates that an epidural blood patch may be successfully used to treat chronic postdural puncture headache 19 months after the initial insult. Even after such a long duration, relief of headache occurred within 30 min, which is a similar time course to that found when epidural blood patch is used within a week after the onset of headache.

The usual history of postdural puncture headache from whatever cause is that it improves with time. Seventy per cent of cases spontaneously improve within 1 week of onset, 95% within 6 weeks, and 96% within 6 months (1). The longest postdural puncture headache previously documented was 12 months (1).

Clinical and experimental data continue to suggest that postdural puncture headache is due to traction of pain-sensitive intracranial structures subsequent to a decrease in cerebrospinal fluid (CSF) pressure caused by leakage of CSF through the subarchnoid-epidural fistula produced by a dural tear (5,9). This is supported by exacerbation of the headache on assuming an upright position, which tends to increase the pressure gradient across the dural tear. Additional support for the etiology of postdural puncture headaches includes the increase in the incidence of postdural puncture headache with increasing needle size (1,9), and the low CSF pressure in patients with postdural puncture headache (1).

Persistent CSF leakage has been demonstrated in two patients with chronic postdural headaches, one 18 weeks (10) and the other 8 months (7) after myelography. In both patients the symptoms disappeared after epidural blood patch (7) or surgical repair of the dural tear (10).

It has also been shown that patients with persistent chronic postlumbar puncture headache have no healing of the cut dural fibers when exposed by laminectomy (10,11), explaining the persistent leakage of CSF.

Animal studies suggest that the normal response to a dural tear is fibroblast proliferation starting at about 48 hr after the injury, and persisting for about 1 week, leading to collagen formation that forms a permanent seal to the tear (12). If the repair process does not occur then the leak may become chronic. An epidural blood patch then acts by forming a gelatinous plug that minimizes or stops the CSF leak, and secondarily promotes fibroblast activity that engulfs the clot and forms a network for collagen deposition to permanently seal the dural tear (12).

Postdural puncture headache is not usually considered in the differential diagnosis of chronic headache, but this report demonstrates that if dural puncture has been performed in the past, this may remain a cause even 19 months after the initial insult. In this situation epidural blood patch should be attempted as both a diagnostic and therapeutic maneuver.

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Postpartum Tubal Ligation Requires More Bupivacaine for Spinal Anesthesia than Does Cesarean Section

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It is sometimes preferable to use regional analgesia rather than general anesthesia for postpartum tubal ligation (PPTL). Either epidural or spinal anesthesia is usually used. A paucity of papers exists regarding the use of spinal anesthesia for PPTL. Therefore, I decided to perform a prospective study to determine the dose requirement of local anesthetic used for spinal anesthesia in the postpartum period.

It is known that for an intraabdominal operation, a sensory level to T-4 is optimal (1). To determine the dose requirement for T-4 dermatomal level in the postpartum period, an arbitrary dose is usually used and the resulting level of anesthesia then determined. The required dose of local anesthetic per blocked segment can then be calculated; thus the total dose to reach the T-4 level can be determined by multiplying the dose per segment by 19 (1 coccygeal + 5 sacrals + 5 lumbars + 8 thoracic segments). It is also known that a gynecologic patient requires a dose of local anesthetic for spinal anesthesia 50% greater than the dose needed to achieve the same dermatomal level in a patient having a cesarean section (CS) (2). Therefore, I arbitrarily chose an initial dose midway between that required for a CS and that for a hysterectomy because the postpartum period is a stage between full-term pregnancy and the nonpregnant state. Accordingly, the dose of bupivacaine chosen in this study was 25% higher than that customarily used for CS. To determine the actual relationship between the dose requirements of bupivacaine for CS and PPTL, a group of CS patients was used as the control group.

Methods and Materials

The study included two groups of patients. Group 1 consisted of 46 parturients having elective repeat CS,

seven of whom had tubal ligation at the time of delivery. Group 2 consisted of 28 patients having PPTL 8–24 hr after delivery. Patients' consents were obtained prior to anesthesia. All patients were ASA class I, and all fetuses were at full-term with no signs of fetal distress. No premedication was administered. All patients received lactated Ringer's solution, 15 mg/kg, over 20 min before injection of local anesthetic into the subarachnoid space, followed by 500 ml during the next 10 min. Thereafter, the infusion rate was 150 ml/hr plus twice the estimated blood loss. The heart rate and the systemic arterial blood pressure were monitored noninvasively by an automatic oscillotonometric cycling device (Dinamap®). The average of the last three readings of pulse and blood presure (BP) taken during the last 3 min prior to induction of anesthesia was considered the baseline level with which all subsequent readings were compared. Hypotension was defined as a decrease in systolic arterial blood pressure equal to or more than 20% of the baseline level.

Spinal anesthesia was induced with the patient in the right lateral horizontal position. Lumbar puncture was performed at the L2–3 interspace using a 26-gauge spinal needle. The anesthetic used was bupivacaine hydrochloride, 0.75%, in 8.25% dextrose, a hyperbaric solution having a specific gravity between 1.030 and 1.035 at 25°C and 1.030 at 37°C (Marcaine® Spinal, manufactured by Winthrop-Breon Laboratories). The dose was calculated according to each patient's height. The dose for CS was 8.25 mg bupivacaine (1.1 ml) for a 150-cm patient with an increase or decrease of 0.25 mg bupivacaine for each 2.5 cm variation above or below that height. The dose for PPTL was increased by 25% above that for CS. The intrathecal injection of the local anesthetic was completed in about 10 sec. After the injection of bupivacaine, the patient was gently turned to the supine horizontal position. Left uterine displacement using an air bag was utilized in the CS group only. The BP and heart rate were monitored every 30 sec to 1 min for the first 15 min; thereafter, every 2 min. The patient was also monitored

Table 1. Patient Data

	CS[a] (n = 46) Mean (± SD)	PPTL[a] (n = 28) Mean (± SD)
Height (cm)	158.1 (6.5)	160.8 (6.3)
Weight (Kg)	79.8 (15.2)	75.7 (16.9)
Age (yr)	28.9 (5.7)	27.6 (4.5)
Gravidity	3.8 (1.6)	4.6 (1.4)
Parity	2.3 (1.1)	4.3 (1.2)[b]

[a]CS, Patients having cesarean sections; PPTL, patients having postpartum tubal ligations
[b]Significant difference, $P < 0.001$.

Table 2. Level of Analgesia—Thoracic Dermatomes

	CS[a] (n = 46) Mean (± SD)	PPTL[a] (n = 28) Mean (± SD)
At 2 min	6.0 (2.8)	7.0 (2.0)
At 5 min	3.9 (2.5)	5.0 (1.7)[b]
At 10 min	2.7 (2.1)	3.8 (1.6)[b]

[a]See Table 1 for explanation.
[b]Significant difference, $P < 0.05$.

using a precordial stethoscope and ECG. Oxygen at a flow rate of 4 L/min was administered through a plastic face mask or nasal cannulae, depending on the patient's preference. Ephedrine, injected intravenously in 10-mg increments, was used to correct maternal hypotension. Morphine in 2.5-mg intravenous (IV) increments was used to treat anxiety, discomfort, or pain. If 15 mg of morphine was unsuccessful in controlling pain, the patient was given general anesthesia using endotracheal intubation after a rapid sequence induction. Morphine was not injected before delivery of the baby.

The times of bupivacaine injection, start of surgery, delivery, and termination of surgery were recorded. The dermatomal level of sensory anesthesia was tested by pin prick at 2, 5, 10, 15, and 20 min after bupivacaine injection. At the same times, motor power was also assessed using the Bromage Scale for Motor Function (0, freely moving lower limb; 1, unable to flex hip; 2, unable to flex hip and knee; 3, complete motor blockade of the lower limb) (3). Time to two-segment regression of the level of sensory anesthesia and the times to complete sensory and motor recovery were determined by examining the patient at 30-min intervals after the initial 20-min observation period.

The degree of analgesia was arbitrarily rated "excellent" if no supplementation was required; "very good" if morphine was required in a dose of 5 mg or less; "good" if the dose was 10 mg or less; and "poor" if the dose exceeded 10 mg or general anesthesia was required.

The dose of bupivacaine per blocked spinal segment was calculated, as was the total dose required to produce a T4-segmental level in each group (as described above).

For statistical analysis, numerical variables (e.g., age, weight, bupivacaine dosage) were compared using a two-sample t-test. When using a categorial variable (e.g., degree of analgesia), a χ^2-test was performed; a P value less than 0.05 was considered statistically significant (4). Data are expressed as means ± SD.

Results

There was no statistical difference between the PPTL and the CS groups in height, weight, age, or gravidity (Table 1). However, parity was more frequent in patients having PPTL ($P < 0.001$). The dermatomal level of anesthesia was not different statistically at the 2-min test after bupivacaine injection. However, it was lower in the PPTL group at 5 and 10 min ($P < 0.05$) (Table 2) despite the larger dose used in the PPTL group (11.32 ± 1.8 mg vs 9.1 ± 0.8 mg, $P < 0.0001$). At 15 and 20 min, the level was not significantly different than the 10-min level in either group. The dose of bupivacaine per segment for PPTL was significantly greater than that for CS (0.56 ± 0.09 mg per segment vs 0.43 ± 0.06 mg per segment, $P < 0.0001$); the ratio between the two was 1.3:1.0. The calculated total dose of bupivacaine required to reach the T-4 level for a PPTL or CS was 10.64 ± 1.71 mg or 8.17 ± 1.14 mg, respectively.

Times for complete motor blockage were similar in CS and in PPTL patients (10.5 ± 2.5 min and 10.1 ± 2.2 min, respectively). There was 92 and 93% "excellent" to "good" analgesia in the CS and PPTL groups, respectively (Table 3). However, there was a tendency, though statistically insignificant, for the frequency of morphine supplementation and the amount of morphine needed to be higher in the CS group, as reflected in the smaller percentage of patients having excellent analgesia.

Ephedrine was needed to correct maternal hypotension in a higher percentage of CS cases than of PPTL cases (83% compared to 7%, respectively, $P < 0.0001$), and the dosage was higher (19.2 ± 14.2 mg compared to 1.6 ± 5.2 mg, respectively, $P < 0.0001$). Also, the incidence of nausea and vomiting was greater with CS (19 and 10% compared to 1 and 0%, respectively, $P < 0.05$).

The time interval from bupivacaine injection to the start of surgery was not different in the two groups, 11.2 ± 3.9 min in the CS group compared to 10.7 ± 3.0 min in the PPTL group. The time interval from the injection of bupivacaine to delivery in the CS group averaged 20.8 ± 5.6 min. As expected, the time from bupivacaine injection to the completion of sugery was

Table 3. Rating of Analgesia

	CS^a (n = 46)	PPTL^a (n = 28)	Statistical significance
Excellent	23 (50%)	20 (72%)	NS
Very good	10 (22%)	4 (14%)	NS
Good	10 (22%)	2 (7%)	NS
Poor	3 (6%)	2 (7%)	NS

^{a}See Table 1 for explanation.

Table 4. Recovery from Anesthesia^a

	CS^b (n = 46) Mean (± SD)	PPTL^b (n = 28) Mean (± SD)
Two-segment regression of level of anesthesia	70.3 (16.3)	73.9 (22.0)
Complete motor recovery	136.7 (35.3)	146.1 (39.4)
Complete sensory recovery	151.7 (42.1)	161.8 (48.2)

No statistical difference between the two groups.
^{a}Minutes.
^{b}See Table 1 for explanation.

longer in the CS group (59.5 ± 12.8 min) than in the PPTL group (37.5 ± 14.4 min, $P < 0.0001$).

Discussion

In the PPTL group, BP was more stable than in the CS group, and ephedrine was rarely used. Therefore, left uterine displacement is not required in PPTL. The greater stability of the cardiovascular system during PPTL than during CS might have been responsible for the negligible incidence of nausea and absence of vomiting in the PPTL group (5).

The degree of analgesia, although statistically insignificant, was clinically evident to be better with PPTL, mainly because of more intraabdominal manipulations with CS associated with previous intraabdominal surgery and possible adhesions.

In two groups of women of comparable age, height, and weight, one undergoing CS and the other PPTL, the ratio between the doses of bupivacaine required to block one spinal segment or reach the T-4 dermatomal level was found to be 1.0:1.3. The decreased requirement of local anesthetic for spinal anesthesia in the full-term pregnant patient is due to two factors: increased sensitivity to the local anesthetic (6,7), and compression of the inferior vena cava leading to shunting of blood through the vertebral canal with subsequent decrease of cerebrospinal volume (8). The increased susceptibility to the local anesthetic can be due to increased progesterone levels (6), increased endorphins (9,10), or increase in CSF pH leading to change in the dissociation of the local anesthetic (11). Plasma progesterone and pregnanediol in humans decrease rapidly after delivery. For example, progesterone levels decreased from 13 to 21 μg/100 ml plasma during labor to zero level when it was estimated at 1–22 hr postpartum (12). After delivery, the size of the uterus is also markedly reduced, thus shunting of blood through the vertebral column and the decreased CSF volume are mostly corrected. CSF production is 20 ml/hr (13). Therefore, in the 8-hr period after delivery, the CSF volume can reach the nonpregnant value. The participation of these two factors,

namely the hormonal and mechanical, is probably responsible for the increased need of the local anesthetic in the postpartum period. However, the individual contribution of each factor in increasing the dose requirement for PPTL compared to CS cannot be determined from this study.

It is well established that the incidence of post-lumbar-puncture headache in parturients is several times greater than in nonpregnant patients having gynecologic operations (14). Therefore, it would have been interesting to know whether the incidence of post-lumbar-puncture headache was different in the CS group and in the PPTL group. Unfortunately, the number of cases in the two groups was too small and the protocol was not designed to answer this question. As a clinical observation, however, none of the patients in either group received an epidural blood patch for management of severe headache. The use of a 26-gauge spinal needle and attention to proper hydration may have been important contributing factors in preventing severe headache.

In conclusion, spinal anesthesia for PPTL is safe and satisfactory. Eight to 24 hours postpartum, the PPTL patient requires 30% more drugs per segment than a patient having an elective repeat CS. The average dose of hyperbaric bupivacaine for PPTL to reach the T-4 level is 10.64 mg for an average patient 158 cm tall weighing 79.8 kg.

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Prestenotic Dilation of the Esophagus:
A Hazard of Internal Jugular Vein Cannulation

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There have been numerous articles about complications of the placement of central venous catheters (CVC) (1–5) via the internal jugular, external jugular, and subclavian veins. We present a complication that has not been previously reported. This complication, though very rare, could have a disastrous outcome.

Case Report

A 17-yr-old girl was admitted to our hospital suffering from severe dysphagia. She had an esophageal stricture that developed after a suicide attempt with a caustic solution. She was thin but not emaciated; blood chemistries, including total protein levels, were normal. Physical examination was normal except for a noticeably marked swallowing reflex, and it was noticed that saliva dribbled from the mouth from time to time.

Barium meal examination showed an almost complete obstruction of the distal ⅚ of the esophagus. There was marked dilation of the prestenotic esophagus that could be seen by x-ray to extend approximately 7 cm above the clavicles (Fig 1). All attempts at esophagoscopy and bouginage failed.

At this stage, she had a gastrostomy for enteral feeding. She was scheduled for esophagectomy and gastric pullthrough procedure. The surgeons decided to insert a CVC via the subclavian route the night prior to surgery. In spite of numerous attempts at cannulation on both sides they were unsuccessful. They then called in the anesthesiologist to perform the procedure.

On his initial examination he noted numerous infraclavicular puncture marks bilaterally and decided to perform a right internal jugular puncture. The left side was unusable because the anastomosis between

the stomach and the remnant esophagus would be performed in the left cervical region.

The mid-anterior approach was used for right internal jugular cannulation (6). A 21-g needle was inserted at the apex of the sternocleidomastoid muscles to locate the vein. Normally the internal jugular vein is found approximately 1 cm under the skin. At a depth of approximately ½ cm, a large amount of clear thick fluid was aspirated. This was initially thought to be an aberrant chylous duct, but because the fluid was not turbid, this assumption was discarded and we decided that we had punctured the esophagus. The needle was removed and redirected laterally. It was again slowly inserted and once again clear thick fluid was aspirated. We decided to perform the usually successful posterior approach, but to our dismay, at 1.5 cm we again entered the esophagus. We decided to abandon the procedure. Approximately 8 hr later the patient complained of upper chest pain, and she developed a fever of 38°C. There was a leukocytosis of 16,000 and a shift to the left. The operation was postponed, and she was put onto large doses of aminoglycosides and a cephalosporin. An infected leak from the esophagus was assumed and possibly a mediastinitis. Her course was stormy and she was obviously septic. Her fever and leukocytosis slowly subsided over the next 10 days, and only then was she scheduled for surgery.

When the esophagus was transected in the neck it was found to be markedly dilated, which confirmed the x-ray diagnosis. Her postoperative course was uneventful except for an atelectasis of the right lower lobe, which was easily treated after a plug was removed by fiberoptic bronchoscopy.

Discussion

The usual complications of CVC are well-documented. Puncture of a dilated esophagus has not to our knowledge been reported, and sepsis resulting from leakage from the esophagus can have serious consequences. Our patient was young, without con-

comitant physical problems, and the outcome was good. In older patients this may not always be the case. Today the esophageal pullthrough procedure is being used increasingly for esophageal pathology (7,8). In view of the complication we encountered, we suggest that the cephalic, basilic, or femoral veins or even a venous cutdown be used; but if the external jugular is easily accessible, this route may also be used. The internal jugular and the subclavian approaches should probably not be used.

In summary, there is danger of esophageal puncture during attempts at right internal jugular cannulation in the presence of prestenotic esophageal dilation, with resulting mediastinitis. Alternate approaches to CVC are suggested to avoid such a hazard.

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Figure 1. The x-ray shows massive prestenotic dilation of the esophagus.

Anesthesia for a Patient with Eosinophilic Myositis

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Eosinophilic myositis is a rare form of inflammatory myopathy. The disease is usually a sequel to parasitic infestation, nonparasitic affection being quite rare. The diagnosis of this condition is based on biopsy of the affected muscle.

We report the anesthetic management of a patient with nonparasitic eosinophilic myositis, and the response to the nondepolarizing muscle relaxant atracurium.

Case Report

A 40-yr-old man weighing 90 kg presented with a 5-month history of weakness in the left leg and cramps in the left calf muscles, which were precipitated by movement. There was no family history of muscle disease.

There was marked hypertrophy of the left calf muscles, but they were not tender. Muscle tone was normal in all limbs. There was no paresthesia or sensory loss. Knee reflexes were brisk in both legs, but ankle jerks were absent. Physical examination was otherwise unremarkable.

Laboratory data showed a total white cell count of 5.1×10^3 with marked eosinophilia of 22%. The hemoglobin level was 15.9 g/dl, and the sickle cell test was positive. Hemoglobin electrophoresis showed that the concentration of Hb A_1, S, and A_2 were 60, 37, and 3%, respectively, indicative of sickle cell trait. Levels of serum electrolytes, blood sugar, BUN, creatinine, SGOT and LDH were within normal limits, but resting serum CPK was elevated to 872 IU/L (normal 30–230 IU/L). Chest x-ray and ECG were normal. The patient was scheduled for muscle biopsy of the left gastrocnemius muscle. Because of elevated CPK it was decided to avoid all known triggering agents of malignant hyperpyrexia (MH) in the anesthetic.

The patient arrived in the operating room with a solution of 5% dextrose in Ringer's lactate running via a peripheral line. Blood pressure was recorded every 5 min with an electronic oscillotonometer (Dinamap). The ECG and rectal temperature were monitored continuously with a Medishield M1 monitor.

The thumb of a restrained arm was attached to a force displacement transducer to record the response of the adductor pollicis to peripheral nerve stimulation of the ulnar nerve via surface electrodes. A myotest nerve stimulator (Biometer) and a continuous pen and paper recorder Myograph 2000 Biometer were used. Train of four (TOF) stimulation of 0.2-msec duration and 2 Hz frequency every 10 sec was used. Anesthesia was induced with fentanyl, 0.2 mg, and thiopental, 400 mg, followed by atracurium, 27 mg (0.3 mg/kg). There was complete suppression of TOF response 7.0 min after administration of atracurium. Laryngoscopy and intubating conditions were adequate, the vocal cords being relaxed, but there was slight coughing after intubation. Anesthesia was maintained with 70% nitrous oxide in oxygen. Ventilation was controlled to maintain normocapnia, and the end-tidal CO_2 was monitored by a Datex Normcap infrared CO_2 analyzer.

There was no response to peripheral nerve stimulation for 30 min after atracurium injection, and the first twitch of TOF reached 10% of the control after 34.2 min. At this time surgery had been completed, so residual neuromuscular block was reversed by neostigmine, 0.035 mg/kg, plus atropine, 0.017 mg/kg. The TOF ratio, the ratio of the fourth response to the first of TOF stimulation, recovered to 0.75 11.25 min after reversal.

Blood pressure, pulse rate, and temperature remained stable during surgery. Intraoperative arterial blood gas tensions were within the normal range. With the return of spontaneous respiration the patient was extubated and sent to the recovery room; further progress was uneventful. A urine sample taken 4 hr postoperatively for myoglobin assay was negative.

The biopsy specimen showed focal degenerative changes with collection of eosinophils consistent with eosinophilic myositis. Tests for possible parasitic infestation were negative, including stool examination

for ova and parasites and measurement of serum Trichinella spiralis, Toxocora, and Ascaris antibodies.

Discussion

Eosinophilic polymyositis is a rare form of inflammatory myopathy. It commonly follows parasitic infestations such as Trichinosis, and is rarely idiopathic in origin. No evidence of parasitic infection was found in this case. The systemic hypereosinophilic syndrome (HES), though rare, is a well-recognized condition (1). It is primarily a disease of middle age, though it may be seen in any age group; males are most affected; and most reported cases have been in Caucasians. HES is characterized by eosinophilia, anemia, hypergammaglobulinemia, cardiac and pulmonary involvement, skin changes, peripheral neuropathy, encephalopathy, and myositis (2). This patient did not have all the features of the syndrome. Agrawal et al. (3) reported a patient with a painless localized muscle tumor due to eosinophilic infiltration. The other abnormalities in this case were an increased level of CPK, eosinophilia, and sickle cell trait. It thus appears that the clinical presentation of eosinophilic myositis may take different forms. The diagnosis can be established only by microscopic examination of the affected muscle. The myositis responds satisfactorily to steroids (1).

We are not aware of any previous reports in the literature on the response of these patients to general anesthesia and muscle relaxants. However, in view of the high level of CPK, it would be wise to avoid all known triggering agents of malignant hyperthermia (MH). The relatively short duration of action of atracurium, and its elimination by Hofmann reaction as well as by enzyme-induced hydrolysis, make it a potentially safer neuromuscular blocking agent in patients with muscle diseases.

The onset of neuromuscular blockade after atracurium is dose-dependent. Basta et al. (4) found that 0.3 mg/kg produces 99% TOF suppression at 2.6 ± 0.9 min. Payne and Hughes (5) showed that intubation was easily accomplished within 1.5 to 2 min with an intravenous bolus of 0.3 mg/kg. In our case, the onset time from injection of an intravenous bolus of

0.3 mg/kg to 100% suppression of TOF was somewhat delayed to 7 min. It is difficult to explain this delay in the onset of neuromuscular blockade.

The duration of action of atracurium, 0.3 mg/kg was also prolonged slightly. The first twitch of TOF recovered to 10% of the control height after 34.2 min, whereas Granstad et al. (6), using the same dose and a similar method of assessing neuromuscular function, reported a duration of action of 27 ± 1.4 min. The slightly longer duration of neuromuscular blockade in this patient suggests that other muscles were involved in the disease, despite the fact that hypertrophy was localized to the left calf muscle.

Atracurium-induced neuromuscular blockade is antagonized readily by neostigmine. Basta et al. (4) found that the time from administration of neostigmine to recovery of 98% control twitch height averaged 8.2 min. In our case, it took 11.24 min after neostigmine for the TOF ratio (the ratio of the fourth response to the first) to recover to 75%.

It would appear that nitrous oxide, oxygen, a non-depolarizing muscle relaxant, and narcotics, with ventilation to ensure good oxygenation is a safe anesthetic technique in patients with eosinophilic myositis. Because of its relatively short duration of action and easy reversibility, atracurium offers advantages over the other non-depolarizing muscle relaxants in these patients.

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Combinations of β-Blockers and Calcium Channel Blockers:
A Cause of Malignant Perioperative Conduction Disturbances?

Barbara L. Hartwell, MD, and Jonathan B. Mark, MD

Many patients are treated for angina pectoris with a combination of a calcium channel blocker and a β-blocking agent. The safety and efficacy of such combination therapy are well-documented (1,2). When considering any modification of this drug regimen preoperatively, most anesthetists elect to continue all antianginal medications until the time of surgery. A recent editorial supports this view (3), and more important, the only prospective study published to date (4) provides a solid basis for this practice.

However, adverse effects have been reported with the use of such combinations, most commonly when verapamil is combined with a β-blocker. Left ventricular dysfunction, bradyarrhythmias, complete heart block, hypotension, and death have all been described (5–7). Furthermore, we now are seeing patients treated with a three-drug regimen consisting of a β-blocker plus two calcium channel blockers (nifedipine plus diltiazem or verapamil). The challenge is to anticipate which patients and which drug combinations present the greatest risk for perioperative hemodynamic problems.

We report a patient with coronary artery disease, chronically treated with nifedipine, diltiazem, and nadolol, who developed malignant bradyarrhythmias and hypotension during anesthetic induction. Hemodynamic restoration required aggressive pharmacologic treatment, including an isoproterenol infusion. The severe conduction problems seen in this patient and the pharmacologic treatment required may have contributed to the patient's early postoperative demise.

Case Report

A 55-yr-old, 85-kg man with a history of hypertension and angina pectoris was scheduled for coronary artery

bypass graft (CABG) surgery. He had no history of myocardial infarction, arrhythmias, or syncope. His preoperative antianginal medications were nadolol, 80 mg daily, and diltiazem, 90 mg, nifedipine, 10 mg, and isosorbide, 20 mg, all four times per day. In addition, he took furosemide, 40 mg, with a potassium supplement because of ankle edema, as well as cimetidine, 400 mg, at bedtime because of a history of peptic ulcer disease and hiatus hernia. His electrocardiogram (ECG) revealed sinus bradycardia with a rate of 40 beats/min and first degree AV block (1° AVB) with a PR interval of 0.22 sec. Cardiac catheterization showed severe three-vessel coronary artery disease. Preoperative blood pressure (BP) was 124/70 mm Hg, and heart rate (HR) was 44 beats/min.

On the morning of surgery, 90 min before induction of anesthesia, the patient received his usual oral morning doses of nadolol, 80 mg, diltiazem, 90 mg, nifedipine, 10 mg, and isosorbide, 20 mg. Additional premedication included cimetidine, 300 mg, morphine, 10 mg, and scopolamine, 0.43 mg, all intramuscularly. The patient was calm and cooperative upon arrival in the operating room; his BP was 90/50 mm Hg and HR was 38 beats/min. ECG monitoring showed the rhythm to be sinus bradycardia. Anesthesia was induced over 10 min with fentanyl, 25 μg/kg intravenously (IV), and pancuronium, 10 mg IV, both administered in small divided doses. During this induction, the patient developed an intermittent junctional bradycardia with a rate of 35–40 beats/min and a systolic blood pressure of 60 mm Hg. He was treated with atropine, a total of 2 mg IV, without any change in heart rate or blood pressure; ephedrine, 22.5 mg IV, also had no effect. After tracheal intubation, an isoproterenol infusion was begun (4–16 μg/min) with a return to sinus rhythm at a rate of 45–55 beats/min and BP of 100/40 mm Hg. Of note, V_5 and limb lead ECG monitoring did not reveal any ischemic ST changes during this prebypass period.

Surgical revascularization was uneventful and weaning from bypass only complicated by a junctional rhythm at 60 beats/min. Atrial pacing was in-

stituted at 80 beats/min. Systolic blood pressure was stable at 90–100 mm Hg. At the end of the procedure, the patient was noted to be asystolic when the pacemaker was transiently turned off to check the intrinsic rhythm. Atrial pacing was continued, and as a safety measure, the patient was transported to the intensive care unit with an isoproterenol infusion at the bedside. His initial postoperative course was unremarkable except for the continued need for atrial pacing. Creatine phosphokinase values and serial ECGs failed to show evidence of perioperative infarction. However, his postoperative ECG showed advanced 1° AVB with an atrial spike—R interval of 0.36 sec. Approximately 22 hr after surgery, the patient was awake and alert and being prepared for extubation when the atrial pacemaker suddenly failed to capture. Ventricular pacing was instituted, but hypotension and a supraventricular tachycardia ensued, rapidly followed by ventricular fibrillation. Cardiopulmonary resuscitation included IV infusions of epinephrine, isoproterenol, calcium, lidocaine, bretylium, and bicarbonate; insertion of an intra-aortic balloon pump; and open chest cardiac massage, with application of new pacing wires. All of these efforts were unsuccessful, and the patient died.

Postmortem examination revealed intact and patent bypass grafts and an area of recent acute subendocardial necrosis (centered posteriorly). Pathological diagnosis proposed this infarction as the cause of death.

Discussion

This case report describes a patient chronically treated with a long-acting nonselective β-adrenergic blocker and two calcium channel blockers. He had severe bradycardia and hypotension before cardiopulmonary bypass and more advanced conduction disturbances after bypass. We believe that these refractory perioperative rhythm and hemodynamic problems were related to the preoperative continuation of his antianginal drug therapy.

Nadolol has been implicated as the cause of prolonged bradycardia in a patient given neostigmine to reverse neuromuscular blockade (8). It is of interest that that patient did not respond to up to 80 μg/min of isoproterenol. This is consistent with the data reported by Dagnino and Prys-Roberts (9) showing that the dose of isoproterenol necessary to accelerate the HR was much greater in patients taking β-blockers than in patients not receiving any drug therapy. Our experience with the patient reported here is consistent with these observations. We were impressed by both the failure of atropine and ephedrine to reverse the

hemodynamic deterioration noted after induction and our unprecedented need for isoproterenol before bypass. Intravenous calcium was not used to treat the prebypass hemodynamic disturbance, as our initial concern was that the patient's rhythm disturbance and hypotension were due to overwhelming β-blockade. Furthermore, if the combination of β-blockers and calcium channel blockers contributed to the hemodynamic instability seen at this time, calcium would not be expected to decrease the prolongation of AV conduction caused by diltiazem (10) whereas β-agonists will reverse such inhibition (11).

The possible additive adverse cardiac effects of β-blockers and calcium channel blockers have been described in the literature (5–7,12). Most warnings have pertained to the exacerbation of congestive heart failure in patients with left ventricular dysfunction (13). However, the occurrence of severe sinus bradycardia and second or third degree heart block with the concurrent use of verapamil or diltiazem and β-blockers has been reported as well (12,14,15). Compensatory reflex sympathetic responses initiated with calcium channel blocker therapy are blunted by β-blockade. Conceivably, the additional sympatholysis induced by premedication or anesthetic induction with fentanyl could have unmasked the harmful hemodynamic depression evidenced in our patient. Whereas other intravenous or inhalation techniques might have produced less bradycardia, fentanyl and pancuronium were selected for induction to minimize further hemodynamic instability and the likelihood of causing myocardial ischemia.

Despite these concerns, the negative chronotropic and dromotropic effects of both β-adrenergic blockers and calcium channel blockers did not adversely affect the patients studied by Henling and associates (4). Their patients had normal preoperative AV conduction and included only one patient taking nadolol and diltiazem. No patient was taking two calcium channel blockers. Although drugs were given until "transport to the operating room," the average interval between the last dose and surgery was 6–8 hr. Henling's patients underwent normothermic bypass, with 30 min of ischemic time, a single dose of cold cardioplegia, and 50 min of total bypass time. Anesthetic techniques involved mainly potent inhaled agents.

Our patient differed from those reported by Henling et al. in many ways. He had first degree AV block before surgery and was taking two calcium channel blockers plus nadolol. He received his preoperative medications only 90 min before induction of anesthesia. Our patient had 47 min of ischemic time and 71 min of moderately hypothermic bypass. Finally, high-dose fentanyl and oxygen was the anesthetic

employed. These differences may explain the exaggerated hemodynamic impairment noted in our patient, and may have placed him at greater risk for perioperative hemodynamic difficulties.

In summary, we report a case of severe perioperative conduction disturbances heralded by intraoperative bradycardia and hypotension refractory to atropine and ephedrine in a patient treated with two calcium channel blockers and a long-acting β-blocker. Whereas the unfortunate postoperative events are not clearly related to the preoperative drug therapy, a note of caution seems justified. One cannot generalize from the data of Henling et al. when patients differ from those in their study. Continuation of all antianginal medications on the day of surgery may not be the best management in all patients receiving combinations of β-blockers and calcium channel blockers. Preoperative heart rate and conduction disturbances must be diligently assessed, and the possibility of temporary modifications of preoperative medical therapy considered.

Our purpose in presenting this report is not to propose rigid guidelines based upon limited anecdotal clinical experience. Instead, we want to point out that the subtleties of preoperative antianginal therapy are critical: optimal timing, dosage, and combinations may have to be individualized until more data from large trials become available. The issue is not *can* full doses of all these drugs and combinations be given until time of surgery, but rather *should* they be given to improve perioperative outcome?

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Addendum

Since submission of this report, the authors have managed two additional cases of junctional bradycardia during anesthestic induction with fentanyl–relaxant–O_2 in patients receiving β-blockers and diltiazem on the morning of surgery. In each case, atropine treatment caused a minor acceleration of the junctional rate without restoration of sinus rhythm.

Spinal Anesthesia Associated with Reversal of Myocardial Ischemia

William F. Urmey, MD, and Donald H. Lambert, PhD, MD

Vasodilation is a means of reducing myocardial oxygen consumption; it is widely employed in the management of angina pectoris (1). Spinal anesthesia is well-recognized as a form of anesthesia that produces both arteriolar and venodilation due to sympathetic blockade (2). Furthermore, in the patient with coronary artery disease who is experiencing pain, the profound analgesia provided by conduction anesthesia may modulate the release of endogenous catecholamines and, therefore, indirectly reduce myocardial oxygen demand. We present a case where spinal anesthesia was associated with reversal of ST-segment depression in a patient with coronary artery disease.

Case Report

A 73-yr-old male with type II diabetes mellitus, hypertension, coronary artery disease, and peripheral vascular disease was scheduled for amputation below the right knee. Four days earlier he had undergone unsuccessful arterial reconstruction of the involved extremity. Preoperative evaluation revealed a history of subendocardial myocardial infarction 2 years earlier with only one subsequent anginal episode, which occurred during a femoral arteriogram 6 months prior to admission. His medications at the time of surgery included chlorpropamide, nifedipine, aspirin, and persantine. The patient had previously undergone several uncomplicated general and spinal anesthetics.

His height was 165 cm, and he weighed 61.3 kg. His blood pressure on admission was 120/80 mm Hg; pulse was 80 and regular. He had a 1/6 systolic ejection murmur. Otherwise, physical examination was notable only for bilaterally decreased pulses below the femoral arteries.

Admission ECG showed left ventricular hypertrophy but was otherwise normal (Fig. 1A). Chest roentgenogram showed no acute disease processes. Other laboratory studies were normal.

Premedication was with oral diazepam, 5 mg, and intramuscular morphine sulfate, 6 mg, approximately 1 hr preoperatively. Upon arrival in the operating room, the patient was in obvious discomfort, complaining of pain due to a cyanotic cold right foot. Further questioning revealed that 15 min prior to premedication he had experienced a 2-min episode of left-sided dull chest pain that had resolved spontaneously. Blood pressure upon arrival in the operating room was 140/80 mm Hg, and pulse was 105 and regular.
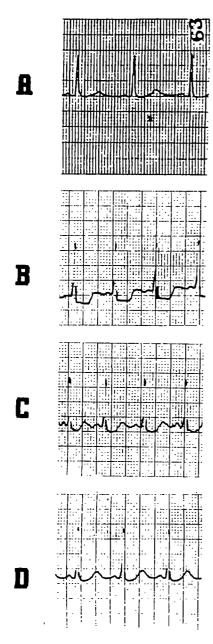
A lead V_5 ECG was obtained (Fig. 1B). This showed 3 mm ST-segment depression, but the patient now denied any chest discomfort. Oxygen was administered via nasal prongs. An isobaric solution of tetracaine (1.5 ml of 1% tetracaine diluted with 1.5 ml normal saline) was injected into the subarachnoid space at the L3–4 interspace.

Within 3 min of injecting the tetracaine, the neurosensory examination by pinprick revealed a level of analgesia below the T10 dermatome. At this point, the ST-depression in V_5 markedly decreased (Fig. 1C). During the next 15 min, the systolic blood pressure (SBP) decreased from 140 to 105 mm Hg, the heart rate (HR) decreased from 105 to 95 beats/min, and the ST-segment depression was nearly completely reversed (Fig. 1D). At this time, the level of analgesia had risen to T7. There were no further changes in SBP or HR for the remainder of the operation.

Approximately 1 hr postoperatively a XII lead ECG showed no ST-segment depression and was not significantly different from the admission ECG. Seven hours after completion of surgery and after complete return of sensory and motor function, the patient was given intramuscular morphine sulfate, 6 mg, and his preoperative dose (20 mg three times per day) of oral nifedipine was restarted. He was comfortable but awakened 5 hr later complaining of dull, left-sided chest pain that was similar in character to that noted preoperatively. At this time his blood pressure was 102/80 mm Hg and HR 96 beats/min. His chest pain was relieved within 5 min with sublinguinal nitro-

Figure 1. Reversal of lead V₅ ST-segment depression after spinal anesthesia. A, on admission; B, prior to spinal anesthesia;' C, 3 min after injection of anesthetic solution; D, 12 min after C. The QRS complexes in B, C, and D have been retouched by hand for clarity without alteration of the ST-segments.

glycerin, 1/200 g. A similar episode of chest pain occurred a few hours later and was again relieved with sublinguinal nitroglycerin, 1/200 g.

Because the patient's HR remained high, varying between 88 and 108, he was started on atenolol. After receiving on oral 50-mg dose of atenolol on the first postoperative day, the patient developed acute congestive heart failure with pulmonary edema and required tracheal intubation and controlled ventila-

tion for 2 days. During this time, he was treated with intravenous digoxin, furosemide, dopamine, and nitroglycerin. With this therapy the patient had no chest pain. There was no evidence of myocardial infarction by serial electrocardiograms and serum creatine phosphokinase isoenzyme levels. Oral isosorbide dinitrate was added to the patient's antianginal regimen, and he was discharged after healing of his surgical incision one month postoperatively.

Discussion

This patient required urgent surgery for an acutely ischemic lower extremity in the presence of evidence of myocardial ischemia. We reasoned that the presence of ischemic limb pain and the attendant probable increase in endogenous catecholamines was contributing to this acute episode of cardiac ischemia. We elected to give a spinal anesthetic. This served to quickly relieve the lower extremity pain. Myocardial oxygen demand was also decreased as evidenced by reversal of ST-segment depression in V₅.

We recognized the potential danger of hypotension associated with spinal anesthesia in the coronary artery disease patient. Acute reduction in arterial blood pressure could have decreased myocardial oxygen supply and worsened the myocardial ischemia. Thus we chose to administer an isobaric solution of tetracaine in an attempt to limit the cephalad spread of the local anesthetic in the subarachnoid space. An unacceptably high sympathetic blockade was thus avoided. We were prepared, however, to treat hypotension immediately had it occurred.

Treatment of myocardial ischemia is directed at optimizing the determinants of myocardial oxygen supply and demand. There are many therapeutic options available to decrease myocardial oxygen consumption (MVo₂) while maintaining adequate myocardial perfusion. These include nitrates (3), β-adrenergic blocking agents (4), general anesthesia (5,6), epidural anesthesia (7), and spinal anesthesia (8). In the emergency patient where airway protection is an important consideration, laryngoscopy and tracheal intubation may be necessary to safely administer general anesthesia. The intubation period has been associated with the onset of myocardial ischemia during general anesthesia (9). A carefully administered regional anesthetic avoids this potentially stressful period as well as emergence, which may also be stressful.

The physiologic responses of the cardiovascular system to spinal anesthesia have been well-described (8,10). These changes are mostly secondary to preganglionic sympathetic denervation. Arterial and arteriolar vasodilation decreases peripheral vascular resistance and cardiac afterload. Sympathetic denervation

of the venous circulation decreases venous return and cardiac preload. In healthy adults undergoing spinal anesthesia, cardiac output and stroke volume have been shown to decrease by an average of 17 and 25%, respectively (2). These changes are mostly the result of decreases in venous return and cardiac preload. Decreased heart rate is often apparent during spinal anesthesia. This occurs as a reflex to decreased atrial distension and/or to blockade of the cardioaccelerator nerves. In this particular case, the patient's SBP decreased to a stable level, approximately 17% below admission level. More than likely, this diminished left ventricular afterload. Heart rate also decreased by approximately 13%. Thus spinal anesthesia rapidly produced a decrease in rate–pressure product, which has been shown to correlate with diminished MVO_2 (11). Furthermore, although filling pressures were not monitored, we presume that decreased preload contributed to reversing the myocardial ischemia.

In summary, spinal anesthesia provided pain relief and sympathetic blockade and thus proved to be an effective anesthetic for this patient with acute preoperative myocardial ischemia.

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(atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:
Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Adults: A Tracrium dose of 0.4 to 0.5 mg/kg (1.7-2.2 times the ED_{95}), given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. No Tracrium dosage adjustments are required for patients with renal disease.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended for adults following the use of succinylcholine for intubation under balanced anesthesia. Further reductions may be desirable with the use of potent inhalation anesthetics. The patient should be permitted to recover from the effects of succinylcholine prior to Tracrium administration. Insufficient data are available for recommendation of a specific initial Tracrium dose for administration following the use of succinylcholine in children and infants.

U.S. Patent No. 4179507   Printed in U.S.A.

TRACRIUM® INJECTION
(atracurium besylate)

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Research Triangle Park
North Carolina 27709

Wellcome

85TRA12B

Albumin & PPF are no safer or more effective than Hespan®
(hetastarch)

...they're simply

As safe as albumin or PPF

In comparative clinical studies, platelet counts, hematocrits, serum fibrinogen levels, prothrombin times (PT), and partial thromboplastin times (PTT) seen with Hespan were comparable to those seen with albumin or plasma protein fraction (PPF).[1,2]

Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.[3-5] As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.[5]

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or cross-matching.[6]

As effective as albumin or PPF

Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.[1-5,7] Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.[1-5,7] And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

Half the price of albumin or PPF

Hespan offers a potential savings to your hospital of tens of thousands of dollars a year.

double the price.

For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

Lifesaving, moneysaving

HESPAN®
(hetastarch)

American Critical Care

American Hospital Supply Corporation

Please see references and brief summary of prescribing information on following page.

References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. Ann Thorac Surg 34 (6):674-679, 1982. 2. Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. Crit Care Med 11 (12):943-945, 1983. 3. Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. Ann Thorac Surg 37 (1):40-46, 1984. 4. Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. Crit Care Med 9 (12):833-837, 1981. 5. Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. Arch Surg 118:804-809, 1983. 6. Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. Transfusion 22 (3):226-228, 1982. 7. Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med 11(11):839-850, 1983.

HESPAN® (hetastarch)

6% Hetastarch in 0.9% Sodium Chloride Injection

CONTRAINDICATIONS
Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS
Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume-expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS
The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS
The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

HOW SUPPLIED
NDC 0094-0037-05-Hespan® (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

CAUTION
Federal (U.S.A.) law prohibits dispensing without prescription. Rev: Feb., 1982

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New...
A significant advance in anesthesia and sedation

One agent for:

- PREMEDICATION
- I.V. CONSCIOUS SEDATION
- INDUCTION AND AS A COMPONENT OF BALANCED ANESTHESIA

For every indication,

Artist's conception of the levels of sedation you can achieve with new VERSED (midazolam HCl/Roche): 1) pre-operative medication, 2) I.V. conscious sedation, 3) induction of anesthesia and as a component of balanced anesthesia.

ROCHE / DU PONT

The advantage in premedication

Virtually painless
faster sedative

on injection...
and amnestic action
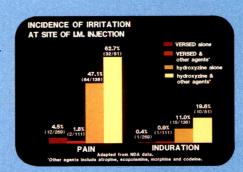
Virtually painless

The first stable water-soluble benzodiaze-pine, VERSED administered intramus-cularly produces less pain, induration or tissue irritation than hydroxyzine I.M.

Sedates faster

In double-blind premedication studies, onset of sedation was significantly faster and more pronounced with VERSED I.M. than with hydroxyzine I.M. After 15 minutes, 43% of 149 patients treated with VERSED had reached the most desirable levels of sedation compared to only 19% of 101 patients treated with hydroxyzine.
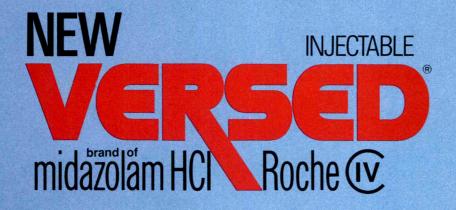
Diminishes recall with a single I.M. injection
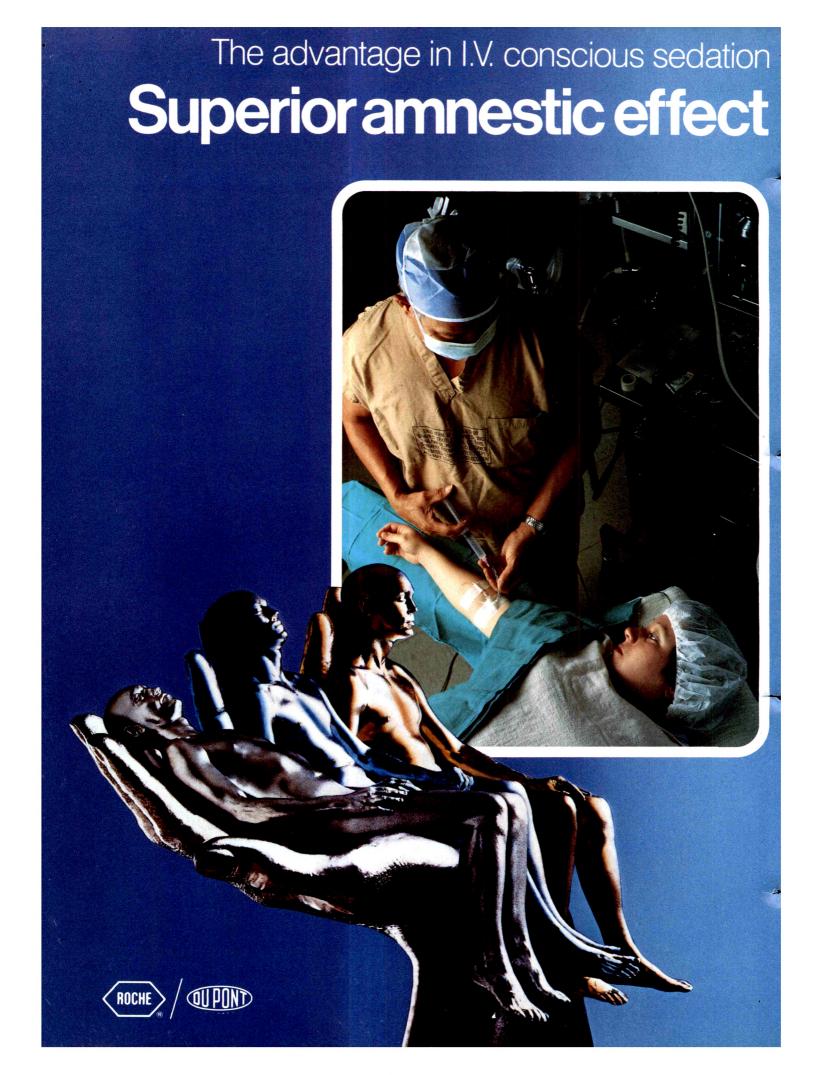
Patients treated with VERSED I.M. had significantly less recall of memory cards (22/71) shown during the preanesthetic period than patients treated with hydroxyzine (70/79). Amnesia was greatest 30 to 60 minutes after administration. And when VERSED was given with scopolamine, the period of diminished recall extended to 90 minutes.

Compatible with other agents in the same syringe

VERSED can be mixed in the same syringe with other frequently used premedicants: morphine sulfate, meperidine, atropine sulfate or scopolamine.
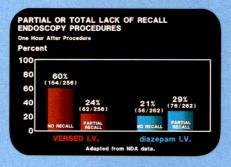
INCIDENCE OF IRRITATION AT SITE OF I.M. INJECTION

- VERSED alone
- VERSED & other agents*
- hydroxyzine alone
- hydroxyzine & other agents*

PAIN — 4.5% (12/269), 1.8% (2/111), 47.1% (64/136), 62.7% (32/51)
INDURATION — 0.4% (1/269), 0.9% (1/111), 11.0% (15/136), 19.6% (10/51)

Adapted from NDA data.
*Other agents include atropine, scopolamine, morphine and codeine.

NEW
INJECTABLE
VERSED®
brand of
midazolam HCl Roche Ⓘⱽ

The advantage in I.V. conscious sedation

Superior amnestic effect

...less tissue irritation

Significantly less recall

In double-blind, multicenter studies, patients treated with VERSED had significantly less recall of endoscopic procedures than patients receiving diazepam. Of 256 VERSED patients, well over half—60%—had no recall of their procedures when questioned one hour later. By contrast, only 21% of 262 diazepam patients had a similar lack of recall.

    Use of a topical anesthetic for peroral procedures and narcotic premedication for bronchoscopies is recommended.

PARTIAL OR TOTAL LACK OF RECALL ENDOSCOPY PROCEDURES
One Hour After Procedure
Percent

VERSED I.V. — NO RECALL 60% (154/256), PARTIAL RECALL 24% (62/256)
diazepam I.V. — NO RECALL 21% (56/262), PARTIAL RECALL 29% (76/262)
Adapted from NDA data.

Less irritation
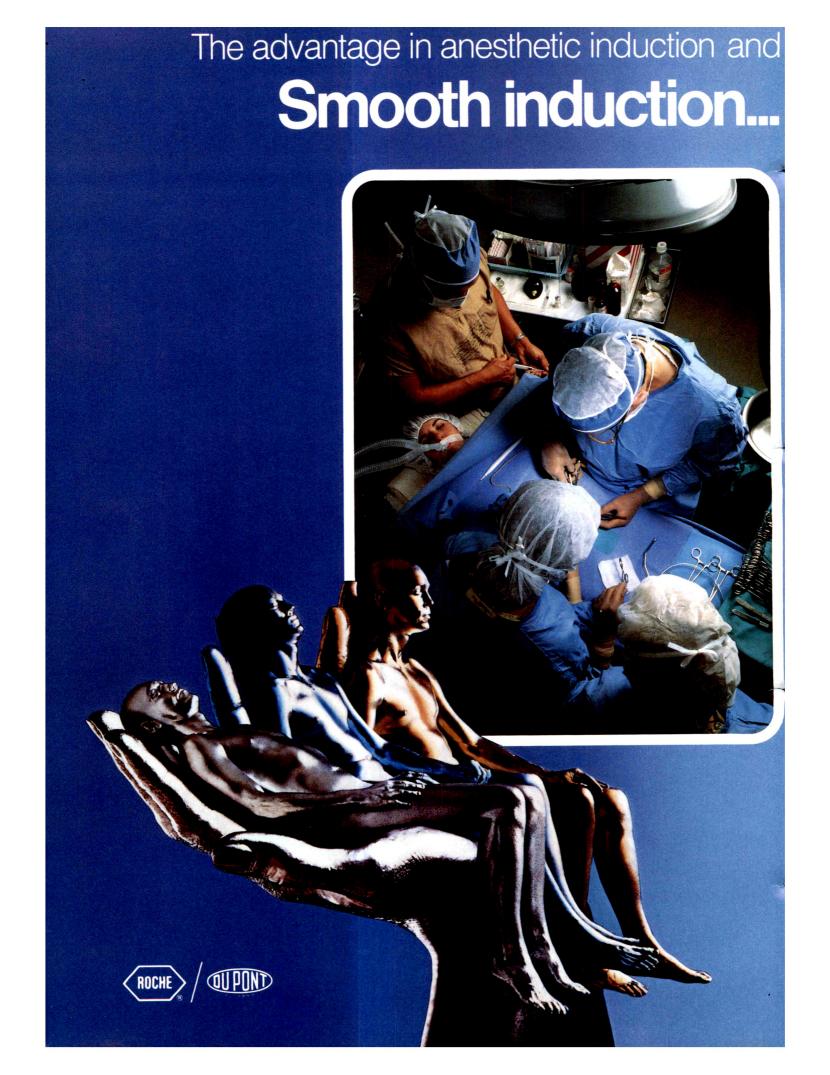
VERSED produced less pain or burning during I.V. administration than diazepam. VERSED also produced less postprocedural irritation: One week following I.V. administration, only 1.4% of 512 patients who received VERSED had tenderness of the vein compared with 3.0% of 503 patients who received diazepam ($P=0.07$).

Faster onset

In the majority of clinical studies, the time required to reach the end point of slurred speech was significantly shorter when patients received VERSED I.V. rather than diazepam I.V. For most procedures, VERSED induced sedation in mean times of 2.8 to 4.8 minutes, while diazepam required mean times of 2.6 to 9.0 minutes.

    As a standard precaution, prior to the I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available and a person skilled in maintaining a patent airway and supporting ventilation should be present. Extra care should be observed in the elderly and debilitated, and in those with limited pulmonary reserve. Dosage of VERSED should be lowered by about 25% to 30% if narcotic premedication is used. Caution patients about driving or operating hazardous machinery after receiving VERSED.

NEW
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VERSED®
brand of midazolam HCl Roche IV

The advantage in anesthetic induction and

Smooth induction...

Dosage and Administration Guidelines

Indication	Usual Adult Dose	Administration
Premedication	0.07-0.08 mg/kg Approx. 5 mg in the average adult.	I.M., deep in a large muscle mass, approx. one hour before surgery. May be mixed with morphine sulfate, meperidine, atropine or scopolamine.
I.V. Conscious Sedation	0.1-0.15 mg/kg is generally adequate, but up to 0.2 mg/kg may be given. Lower dosage by 25-30% when narcotic premedication is given. Patients over 60 require lower doses—reduce by 30%. Increments of 25% of initial dose to maintain desired level of sedation.	Slow I.V. administration into a large vein; titrate to desired sedative end point, *i.e., slurred speech*. Administer immediately before the procedure. Use of a topical anesthetic for peroral procedures and narcotic premedication for bronchoscopies is recommended. IMPORTANT: Start with the lowest dose of the range and titrate slowly.
Induction	**Premedicated Patients** Range: 0.15-0.35 mg/kg Average adult under 55: 0.25 mg/kg Over 55, ASA I or II: initial dose of 0.2 mg/kg ASA III or IV: 0.15 mg/kg **Unpremedicated Patients** Average adult under 55: 0.3-0.35 mg/kg initially, up to 0.6 mg/kg Over 55: initial dose of 0.3 mg/kg ASA III or IV: initial dose of 0.2-0.25 mg/kg Minimum dose of 0.15 mg/kg	Slow I.V. administration into a large vein. IMPORTANT: Start with the lowest dose of the range and titrate slowly. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used.
As a component of balanced anesthesia for short surgical procedures	Approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.	

VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; however, they may be used in patients with open angle glaucoma only if they are receiving appropriate therapy.

Titrate to desired effect

ROCHE / DUPONT

NEW

INJECTABLE

VERSED

brand of
midazolam HCl   Roche IV

VERSED® (brand of midazolam HCl/Roche) INJECTABLE ℞

DESCRIPTION: VERSED (brand of midazolam hydrochloride/Roche) is a water-soluble benzodiazepine available as a sterile parenteral dosage form for intravenous or intramuscular injection. Each ml contains midazolam hydrochloride equivalent to 5 mg midazolam compounded with 0.8% sodium chloride and 0.01% disodium edetate, with 1% benzyl alcohol as preservative; the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

Chemically, midazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a] [1,4]benzodiazepine. It is a white to light yellow crystalline compound, insoluble in water; the hydrochloride salt is soluble in aqueous solutions. Midazolam has a calculated molecular weight of 325.78.

CLINICAL PHARMACOLOGY: VERSED is a short-acting benzodiazepine central nervous system depressant.

The effects of VERSED on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other premedications. Onset time of sedative effects after IM administration was 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. In one study, when tested the following day, 73% of the patients who received VERSED intramuscularly had no recall of memory cards shown 30 minutes following drug administration; 40% had no recall of the memory cards shown 60 minutes following drug administration.

Sedation after IV injection was achieved within 3 to 5 minutes; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the patients in the endoscopy studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope.

When VERSED is given intravenously as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or with sedative premedication. Some impairment in a test of memory was noted in 90% of the patients studied.

VERSED, used as directed, does not delay awakening from general anesthesia. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline Trieger competency) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared with patients who received thiopental, patients who received midazolam generally recovered at a slightly slower rate. Reaction time under stress (operating automobiles or other hazardous machinery) has not been studied. (See WARNINGS.)

The intravenous administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

In patients without intracranial lesions, induction with VERSED is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that seen following use of thiopental. Preliminary data in intracranial surgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with VERSED and with thiopental during intubation.

Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with VERSED; patients with glaucoma have not been studied.

Usual intramuscular premedicating doses of VERSED do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent. Induction doses of VERSED depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental. Impairment of ventilatory response to carbon dioxide is more marked in patients with chronic obstructive pulmonary disease (COPD). Sedation with intravenous VERSED does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (Vmax) increase. In cardiac hemodynamic studies, induction with VERSED was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (e.g., 85/minute) tended to slow slightly.

The following preliminary pharmacokinetic data for midazolam have been reported. In normal subjects and healthy patients intravenous midazolam exhibited an elimination half-life of 1.2 to 12.3 hours, a large volume of distribution (0.95 to 6.6 L/kg) and a plasma clearance of 0.15 to 0.77 L/hr/kg.

Following intravenous administration, less than 0.03% of the dose is excreted in the urine as intact midazolam. Midazolam is rapidly metabolized to 1-hydroxymethyl midazolam which is conjugated with subsequent excretion in the urine. Approximately 45% to 57% of the dose is excreted in the urine as the conjugate of 1-hydroxymethyl midazolam, the major metabolite of midazolam. The half-life of elimination of 1-hydroxymethyl midazolam is similar to the parent compound. The concentration of midazolam is 10- to 30-fold greater than that of 1-hydroxymethyl midazolam after single IV administration.

Clinical effects of VERSED do not directly correlate with the blood concentrations of midazolam.

In a small group of patients (n = 11) with congestive heart failure, there appeared to be a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam; however, the total body clearance of midazolam appeared to remain unchanged at a single 5-mg intravenous dose. There was no apparent change in the pharmacokinetic profile following the intravenous administration of 5 mg of midazolam to a small group of patients (n = 12) with hepatic dysfunction. There was a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution in a small group of patients (n = 15) with chronic renal failure.

In a small group (n = 12) of surgical patients, aged 49 to 60 years old, given 0.2 mg/kg midazolam intravenously, there appeared to be a small increase in the volume of distribution and elimination half-life with little change in total body clearance compared to an equal number of younger surgical patients (aged 18 to 30).

VERSED® (brand of midazolam HCl/Roche) INJECTABLE

The mean absolute bioavailability of midazolam following intramuscular administration is greater than 90%. The mean time of maximum midazolam plasma concentrations following intramuscular dosing occurs within 45 minutes postadministration. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after intramuscular administration are about one-half of those achieved after equivalent intravenous doses. The pharmacokinetic profile of elimination after intramuscularly administered midazolam is comparable to that observed following intravenous administration of the drug. Dose-linearity relationships have not been adequately defined.

Midazolam is approximately 97% plasma protein-bound in normal subjects and patients with renal failure. In animals, midazolam has been shown to cross the blood-brain barrier. In animals and in humans, midazolam has been shown to cross the placenta and enter into fetal circulation. It is not known whether midazolam is excreted in human milk.

INDICATIONS: Injectable VERSED is indicated—
● intramuscularly for preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of peri-operative events;
● intravenously as an agent for conscious sedation prior to short diagnostic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and cardiac catheterization, either alone or with a narcotic;
● intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous VERSED can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures; longer procedures have not been studied.

When used intravenously, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours. (See CLINICAL PHARMACOLOGY.)

CONTRAINDICATIONS: Injectable VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy. (See CLINICAL PHARMACOLOGY.)

WARNINGS: PRIOR TO THE INTRAVENOUS ADMINISTRATION OF VERSED IN ANY DOSE, THE IMMEDIATE AVAILABILITY OF OXYGEN AND RESUSCITATIVE EQUIPMENT FOR THE MAINTENANCE OF A PATENT AIRWAY AND SUPPORT OF VENTILATION SHOULD BE ENSURED. Because intravenous VERSED depresses respiration (see CLINICAL PHARMACOLOGY) and because opioid agonists and other sedatives can add to this depression, VERSED should be administered as an induction agent only by a person trained in general anesthesia and should be used in conscious sedation only when a person skilled in maintaining a patent airway and supporting ventilation is present.

Injectable VERSED should not be administered to patients in shock or coma, or in acute alcohol intoxication with depression of vital signs.

The hazards of intra-arterial injection of VERSED solutions in humans are unknown; therefore, extreme precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

Higher risk surgical patients or debilitated patients require lower dosages for induction of anesthesia, whether premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over the age of 55 years require lower dosages for induction of anesthesia, whether premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduced initial dosage of VERSED is recommended and the possibility of profound and/or prolonged effect should be considered.

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with a narcotic.

The decision as to when patients who have received injectable VERSED, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle, must be individualized. Gross tests of recovery from the effects of VERSED (see CLINICAL PHARMACOLOGY) cannot be relied upon alone to predict reaction time under stress. This drug is never used alone during anesthesia and the contribution of other peri-operative drugs and events can vary. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia and surgery, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS: General: Because an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended. The use of narcotic premedication is recommended for bronchoscopies. Intravenous doses of VERSED should be decreased by 25% to 30% for elderly and debilitated patients. (See WARNINGS and DOSAGE AND ADMINISTRATION.) These patients will also probably take longer to recover completely after VERSED administration for the induction of anesthesia.

VERSED does not protect against the increase in intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:
1. Inform your physician about any alcohol consumption and medicine you are now taking, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine and fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, the dosage of VERSED should be adjusted according to the type and amount of premedication administered. (See DOSAGE AND ADMINISTRATION.)

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia. (See CLINICAL PHARMACOLOGY.)

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

Carcinogenesis, mutagenesis, impairment of fertility:
Carcinogenesis: Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.
Mutagenesis: Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.
Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 10 times the human IV dose of 0.35 mg/kg.
Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.
Segment II teratology studies, performed with midazolam maleate injectable in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.
Nonteratogenic effects: Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.
Labor and delivery: In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.
The use of injectable VERSED in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.
Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.
Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.
ADVERSE REACTIONS: Fluctuations in vital signs were the most frequently seen findings following parenteral administration of VERSED and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. These are common occurrences during anesthesia and surgery and are affected by the lightening or deepening of anesthesia, instrumentation, intubation and use of concomitant drugs.
In the conscious sedation studies, hypotension occurred more frequently after IV administration of VERSED in patients concurrently premedicated with meperidine. It should especially be noted that VERSED does not modify the circulatory effects of neuromuscular blocking agents or the tachycardia and blood pressure rises seen during endotracheal intubation under light general anesthesia. During the clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.
The following adverse reactions were reported after intramuscular administration:

headache (1.3%)	*Local effects at IM injection site*
	pain (3.7%)
	induration (0.5%)
	redness (0.5%)
	muscle stiffness (0.3%)

The following adverse reactions were reported subsequent to intravenous administration:

hiccoughs (3.9%)	*Local effects at the IV site*
nausea (2.8%)	tenderness (5.6%)
vomiting (2.6%)	pain during injection (5.0%)
coughing (1.3%)	redness (2.6%)
"oversedation" (1.6%)	induration (1.7%)
headache (1.5%)	phlebitis (0.4%)
drowsiness (1.2%)	

Other adverse experiences, observed mainly following IV injection and occurring at an incidence of less than 1.0%, are as follows:
Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea.
Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm.
Gastrointestinal: Acid taste, excessive salivation, retching.
CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia.
Special Sense: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness.
Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus.
Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.
DRUG ABUSE AND DEPENDENCE: Midazolam is subject to Schedule IV control under the Controlled Substances Act of 1970.
Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs.
Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.
OVERDOSAGE: There have been no reports of injectable VERSED overdosage. The manifestations of VERSED overdosage are expected to be similar to those observed with other benzodiazepines and include sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from VERSED overdosage would be expected.
Treatment of overdosage: Treatment of injectable VERSED overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdosage.
DOSAGE AND ADMINISTRATION: Dosage should be individualized. In general, lower doses are required in elderly or debilitated patients. The dosage of intravenous VERSED administered should be adjusted according to the type and amount of premedication used. When intravenous use is indicated, oxygen, resuscitative equipment and personnel resources for the maintenance of a patent airway should be immediately available. (See WARNINGS.)
Injectable VERSED may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Injectable VERSED is compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.
For *intramuscular* use, VERSED should be injected deep in a large muscle mass. *Intravenous* VERSED for conscious sedation should be administered slowly; rapid injection may cause respiratory depression or apnea requiring assisted or controlled ventilation. For induction of general anesthesia, the initial dose should be administered over 20 to 30 seconds for optimum effect. Extreme care should be taken to avoid intra-arterial injection or extravasation (see WARNINGS).

INTRAMUSCULARLY
For preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of peri-operative events.

INTRAVENOUSLY
Endoscopic or Cardiovascular Procedures
For conscious sedation, VERSED can be used either alone or together with a narcotic immediately before the procedure with supplemental doses of VERSED to maintain the desired level of sedation throughout the procedure. For peroral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.

Induction of Anesthesia
For induction of general anesthesia, before administration of other anesthetic agents.

USUAL ADULT DOSE
For premedication the recommended dose of VERSED is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM for an average adult) approximately one hour before surgery. Onset is within 15 minutes, peaking at 30 to 60 minutes. It can be administered concomitantly with atropine sulfate or scopolamine hydrochloride and reduced doses of narcotics.

Titrate dosage to desired sedative end point, *i.e.*, slurring of speech, with slow administration immediately prior to the procedure. Generally 0.1 to 0.15 mg/kg is adequate, but up to 0.2 mg/kg may be given, particularly when concomitant narcotics are omitted. Doses in excess of 0.15 mg/kg may result in increased risk of respiratory depression or drowsiness in elderly or debilitated patients. Additional maintenance doses may be given in increments of 25% of the initial dose to maintain the desired level of sedation.
Narcotic premedication results in less variability in patient response. Dosage should be lowered by about 25% to 30% if narcotic premedication is used. Patients 60 years or older may require lower doses (by about 30%) than younger patients.

Individual response to the drug is variable, particularly when a narcotic premedication is not used. The dosage should be titrated to the desired effect according to the patient's age and clinical status.
Unpremedicated Patients
In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3 to 0.35 mg/kg for induction, administered over 20 to 30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used; induction may instead be completed with volatile liquid inhalational anesthetics. In resistant cases, up to 0.6 mg/kg total dose may be used for induction, but such larger doses may prolong recovery.
Unpremedicated patients over the age of 55 years usually require less VERSED for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less VERSED for induction. An initial dose of 0.2 to 0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice.
Premedicated Patients
When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15 to 0.35 mg/kg.
In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20 to 30 seconds and allowing 2 minutes for effect, will usually suffice.
The initial dose of 0.2 mg/kg is recommended for good risk (ASA I and II) surgical patients over the age of 55 years.
In some patients with severe systemic disease or debilitation, as little as 0.15 mg/kg may suffice. Narcotic premedication frequently used during clinical trials included fentanyl (1.5 to 2 μg/kg IV, administered 5 minutes before induction), morphine (dosage individualized, up to 0.15 mg/kg IM), meperidine (dosage individualized, up to 1 mg/kg IM) and Innovar (0.02 ml/kg IM). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for intravenous fentanyl, administered 5 minutes before induction, all other premedications should be administered approximately one hour prior to the time anticipated for VERSED induction

Injectable VERSED can also be used during maintenance of anesthesia, *for short surgical procedures*, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases. Long surgical procedures have not been studied.
Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
HOW SUPPLIED: All package configurations contain midazolam hydrochloride equivalent to 5 mg midazolam/ml.
2 ml vials (10 mg)—boxes of 10 (NDC 0004-1973-01);
5 ml vials (25 mg)—boxes of 10 (NDC 0004-1975-01);
10 ml vials (50 mg)—boxes of 10 (NDC 0004-1946-01);
2 ml Tel-E-Ject® disposable syringes (10 mg)—boxes of 10 (NDC 0004-1947-01).
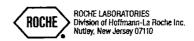
Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

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NITROUS OXIDE/N$_2$O

Editor: Edmond I. Eger II, M.D., Professor and Vice Chairman for Research, Department of Anesthesia, University of California, San Francisco

After 140 years of use, nitrous oxide is now known to be more than an inert vehicle for other, more potent anesthetics. Nitrous oxide affects the function of every body tissue significantly. Optimum application requires a full appreciation of both the benefits and potential hazards of this anesthetic substance.

Nitrous Oxide/N$_2$O is a complete resource on the subject. It describes what is known about nitrous oxide — applications and contraindications — and debates its continued clinical use. The current clinical applications of N$_2$O are reviewed by means of:

- thorough discussion of N$_2$O pharmacology and distribution
- detailed summary of known side effects and toxicity
- practical guidelines for avoiding and managing these effects

Finally, the case for administering this anesthetic is carefully and candidly assessed in chapters by proponents of both views. **Nitrous Oxide/N$_2$O** is a controversial work that everyone using the drug will want to read.

Contents. Preface. Contributors. A History of Nitrous Oxide. Physics, Chemistry, and Manufacture of Nitrous Oxide. Nitrous Oxide Analgesia. MAC. Nitrous Oxide Delivery Systems. Pharmacokinetics. Respiratory Effects of Nitrous Oxide. Cardiovascular Effects of Nitrous Oxide. Central Nervous System Effects of Nitrous Oxide. Neuromuscular Effects of Nitrous Oxide. Nitrous Oxide in Obstetrics. Metabolism of Nitrous Oxide. Nitrous Oxide Inactivates Methionine Synthetase. Mutagenicity, Carcinogenicity, and Teratogenicity of Nitrous Oxide. Nitrous Oxide Abuse. Toxicity of Nitrous Oxide. The Use of Nitrous Oxide by Dentists. Nitrous Oxide in Veterinary Practice and Animal Research. Controlling Occupational Exposure to Nitrous Oxide. Should We Not Use Nitrous Oxide. We Should Continue to Use Nitrous Oxide. Epilogue. Index.

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Contents

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INDICATIONS: INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE* (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.
If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.
The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the

patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.
Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.
Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.
INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.
When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.
Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.
Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.
Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).
When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated, respiratory arrest could occur.
Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.
Vital signs should be monitored routinely.
Usual Adult Dosage
I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.
II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
If INNOVAR* injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.
III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.
IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.
How Supplied: *2 ml. and 5 ml. ampoules*—packages of 10; *10 ml. multiple-dose vials*—packages of 10.
U.S. Patent No. 3,161,645.
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REFERENCES: 1. Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Anal* 1974;53:361-364. **2.** Tornetta FJ: A comparison of droperidol, diazepam, and hydroxyzine hydrochloride as premedication. *Anesth Anal* 1977;56:496-500. **3.** Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Curr Ther Res* 1984;35:715-720.
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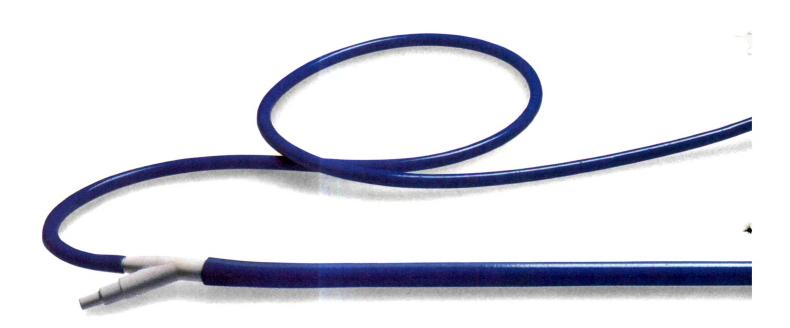
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The cost of brain monitoring versus the cost of brain damage.

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The technology to monitor brain function during major surgery already exists — and not just in the primitive form most physicians are accustomed to.

There is a brain monitor that can provide the same continuous information as a 16-channel (whole-head) EEG. A monitor that can operate without special technical expertise or attention. A monitor whose built-in computer can sound a timely warning of the smallest irregularities before they become irreversible.

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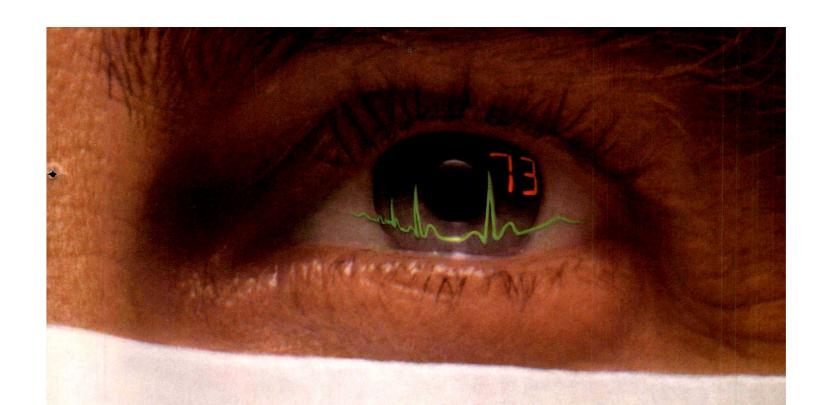
But in today's environment of changing medical expectations, the very availability of this sort of brain-monitoring equipment presents a host of issues — professional, ethical, financial and humane — that demand thoughtful consideration.

We urge you to discuss the pros and cons of brain monitoring with your colleagues.
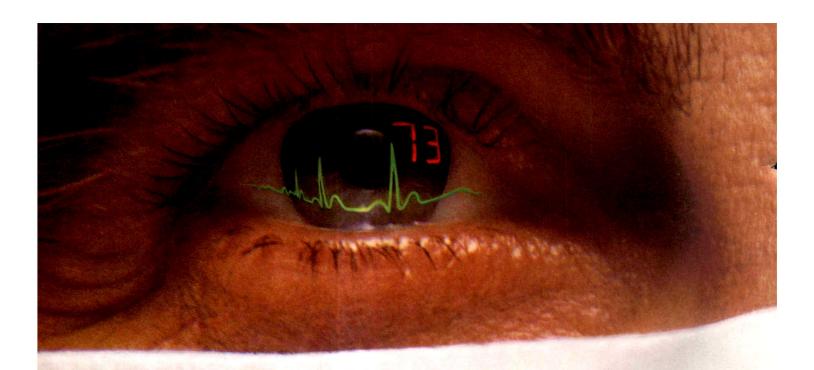
And we invite you to tell us what you think. Write CNS, Inc., 10349 W. 70th Street, Minneapolis, Minnesota 55344, or call 800-328-8322 ext. 120. If you request, we will be happy to send you more information on brain monitoring.

CNS

See for yourself.

The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...
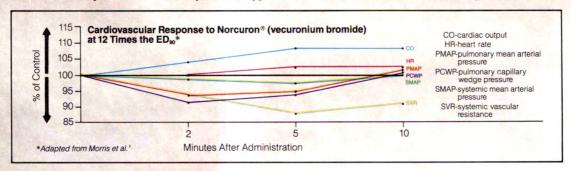
ideal for your patients, including those at risk.[1-5]

See the safety for yourself.

Free of clinically significant cardiovascular effects.*
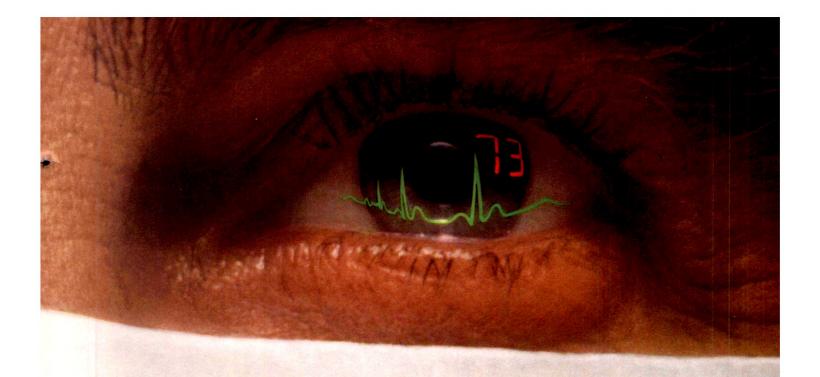
NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.[1-4] In fact, even at 12 times effective doses, under halothane anesthesia,[1] NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.

Cardiovascular Response to Norcuron® (vecuronium bromide) at 12 Times the ED_{90}*

% of Control (y-axis: 85 to 115)
Minutes After Administration (x-axis: 2, 5, 10)

Curves: CO, HR, PMAP, PCWP, SMAP, SVR

- CO-cardiac output
- HR-heart rate
- PMAP-pulmonary mean arterial pressure
- PCWP-pulmonary capillary wedge pressure
- SMAP-systemic mean arterial pressure
- SVR-systemic vascular resistance

*Adapted from Morris et al.[1]

Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED_{95}.[5]
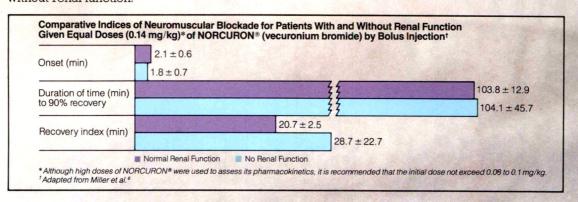
NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.[5]

The Effect of Nondepolarizing Muscle Relaxants* Percent of Control

Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5†	2	212	79	119
Atracurium	0.6†	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2	3.5	87	99	102

*Adapted from Basta et al.[5]
†0.1 mg/kg higher than recommended dose.

Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†

	Normal Renal Function	No Renal Function
Onset (min)	2.1 ± 0.6	1.8 ± 0.7
Duration of time (min) to 90% recovery	103.8 ± 12.9	104.1 ± 45.7
Recovery index (min)	20.7 ± 2.5	28.7 ± 22.7

■ Normal Renal Function   ■ No Renal Function

*Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.
†Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®
(vecuronium bromide) injection

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide)*. Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED90 (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain theshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED90) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution	5% glucose in saline
5% glucose in water	Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC#0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC#0052-0442-57).
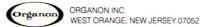
STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.   SINGLE USE VIALS.
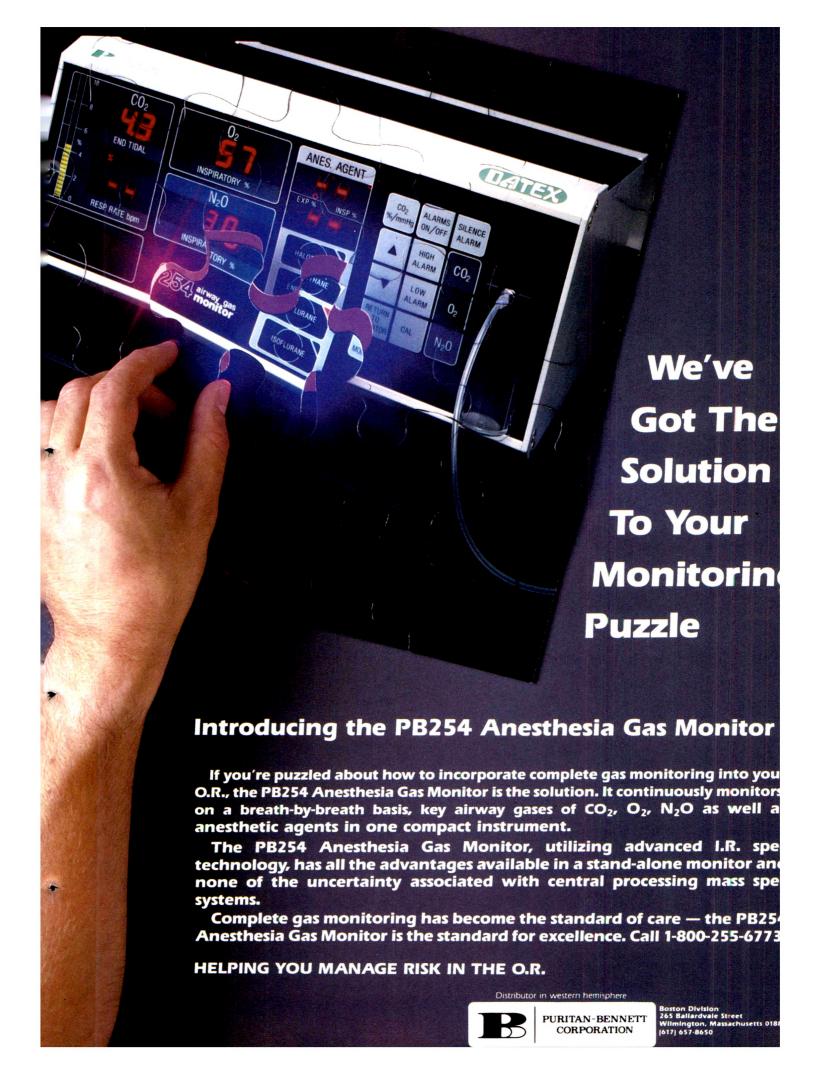Manufactured for ORGANON INC. by BEN VENUE LABORATORIES, INC., Bedford, OH 44146   ISSUED 5/86

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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1986 Awards

The Board of Trustees of the IARS is pleased to advise that four Awards were granted and announced at the March 1986 meeting in Las Vegas, as follows:

Zeljko J. Bosnjak, PhD, Medical College of Wisconsin, Milwaukee, WI:
  "Effects of Chronic Administration of Calcium Antagonists"
John F. Butterworth IV, MD, Bowman Gray School of Medicine, Winston-Salem, NC:
  "Brain Cellular Mechanisms of Increased Anesthetic Susceptibility with Aging"
Philippe R. Housmans, MD, PhD, Mayo Foundation, Rochester, MN:
  "Influence of Halothane on Intracellular Calcium Handling in Mammalian Cardiac Muscle"
Vladimir Nigrovic, MD, Medical College of Ohio, Toledo, OH:
  "Adverse Reactions and Metabolism of Atracurium"

1987 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

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• The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.

• The applicant must be a member of the International Anesthesia Research Society.

• Applications must be received in the IARS Cleveland office no later than December 15, 1986.

• The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

> International Anesthesia Research Society
> 3645 Warrensville Center Rd.
> Cleveland, OH 44122
> Telephone: (216) 295-1124

The 1987 Award(s) will be announced at the Annual Scientific Meeting (61st Congress) of the International Anesthesia Research Society to be held at the Buena Vista Palace, Lake Buena Vista (Orlando), Florida, March 14-18, 1987.

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Comparison of Lidocaine and Bupivacaine Depression of Sinoatrial Nodal Activity during Hypoxia and Acidosis in Adult and Neonatal Guinea Pigs

Zeljko J. Bosnjak, PhD, David F. Stowe, MD, PhD, and John P. Kampine, MD, PhD

BOSNJAK ZJ, STOWE DF, KAMPINE JP. Comparison of lidocaine and bupivacaine depression of sinoatrial nodal activity during hypoxia and acidosis in adult and neonatal guinea pigs. Anesth Analg 1986;65:911–7.

High blood concentrations of local anesthetics are cardiotoxic. The aim of this study was to compare the effects of lidocaine and bupivacaine on the intrinsic pacemaker activity of in vitro sinoatrial nodal cells of the adult and neonatal guinea pig in the presence and absence of hypoxia and acidosis. Fifteen pairs of adult (>80 days old) and neonatal (0–3 days old) hearts were isolated. Nodal tissues were suffused with Krebs–Ringer solution at 37°C and exposed to increasing concentrations of either lidocaine (0.05–0.8 mM) or bupivacaine (0.01–0.4 mM). The suffusate was equilibrated either with 5% CO_2, 95% O_2 (pH 7.40, PO_2 482 torr) or with 12% CO_2, 88% N_2 (pH 7.01, PO_2 58 torr). Transmembrane action potentials were recorded from sinoatrial nodal cells and impulse intervals were converted to rates. We found that hypoxia and acidosis alone reduced rates in both adults and neonates, and that the reduction was additive to the effects of local anesthetics. Bupivacaine was 4–5 times more potent in decreasing rates than was lidocaine in both age groups. Lidocaine was about twice as effective in depressing neonatal rates as adult rates, and bupivacaine caused cessation of pacemaker activity in a greater percentage of nodes than did lidocaine. Our results demonstrate, in vitro, that the neonatal sinoatrial node is more sensitive to lidocaine and bupivacaine than is the adult node, that bupivacaine is more potent in depressing and stopping nodal activity, and that hypoxia and acidosis enhance pacemaker depression caused by these agents. These findings may explain the fetal bradycardia, especially with fetal hypoxia and acidosis, observed with maternal intravenous injection of local anesthetics during labor.

Key Words: ANESTHETICS, LOCAL—bupivacaine, lidocaine. HEART—bupivacaine, lidocaine toxicity.

Local anesthetics can, in high enough blood concentrations, cause seizures and circulatory collapse. Accidental intravascular injection of a large dose of bupivacaine during regional anesthesia in humans results in convulsions with concomitant hypoxemia, acidemia, cardiac dysrhythmias, and circulatory collapse (1–5). In human parturients epidural injection of bupivacaine produces a greater incidence of fetal heart decelerations than does an amount of lidocaine three times greater (6,7). Pericervical block with bupivacaine is also frequently accompanied by fetal bradycardia (8).

Animal studies have contributed to an understanding of the relative cardiotoxicities of the more lipid-soluble, longer acting amide anesthetic agents such as bupivacaine and the less lipid-soluble, shorter acting amide agents such as lidocaine. For example, in adult sheep the intravenous infusion dose of bupivacaine necessary to cause cardiovascular collapse (greater than that required to produce convulsions) in the presence of hypoxia and acidemia is about half that required for lidocaine (9). In ventilated cats subconvulsant doses of bupivacaine precipitate nodal and ventricular dysrhythmias whereas subconvulsant doses of lidocaine do not (10). Cardiotoxic effects of bupivacaine observed in intact dogs include increased conduction time of the atria, prolonged atrial ventricular nodal refractory periods, decreased left ventricular contractility, ventricular tachyarrhythmias, and electromechanical dissociation (11,12). In the isolated rat heart preparation, bupivacaine is more potent than

lidocaine in decreasing the atrial rate and delaying atrial-ventricular conduction (13). In isolated heart tissue from guinea pigs, bupivacaine is 6–10 times more potent than lidocaine in decreasing heart rate, contractility, and myocardial oxygen consumption (14,15); the combination of acidosis and hypoxia enhances the bradycardic effect of bupivacaine more than lidocaine (16).

The comparative effects of lidocaine and bupivacaine on depressing automaticity and impulse formation in the adult and neonatal sinoatrial node have not been described; neither have the added effects of hypoxia and acidosis that often accompany the cardiovascular effects of toxic doses of local anesthetic agents in vivo. The frequent use of bupivacaine for regional anesthesia in obstetrics, the common association of hypoxia and acidosis with cardiotoxicity, and the observation of fetal bradycardia with transplacental passage of local anesthetics (8,17–19) led us to study the relative sensitivity of the intrinsic cardiac pacemaker to lidocaine and bupivacaine. In this report we compare the effect of these two agents on pacemaker cell activity in isolated sinoatrial nodal tissue of the adult and neonatal guinea pig, and we have also examined the additional effects of hypoxia and acidosis.

Methods

The hearts of 15 adult (>80 days old) and 15 neonatal (0–3 days old) English shorthair guinea pigs were isolated after killing the animals by decapitation. The region of the sinoatrial node was excised and fixed to the floor of the suffusion bath with the luminal surface upward. In each experiment the bath contained sinoatrial nodal tissues of an adult and a neonate, so that they were always exposed to identical experimental conditions. Transmembrane action potentials were recorded simultaneously from each nodal tissue using standard electrophysiological techniques. Our methods of identifying, recording, and analyzing action potentials from the sinoatrial node have been described previously (20). The intervals, in milliseconds, between spontaneously generated action potentials were measured from the maximal slope of the phase 0 depolarization and were converted to rates (beats/min).
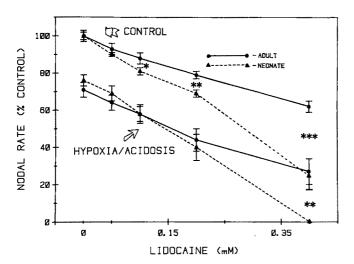
The suffusate solution (Krebs–Ringer) contained the following: NaCl, 136 mM; KCl, 5.9 mM; MgCl₂, 1.2 mM; CaCl₂, 2.5 mM; NaH₂PO₄, 1.2 mM; NaHCO₃, 15.5 mM; and glucose, 11 mM. During control periods the solution was equilibrated with 5% CO_2, 95% O_2. Hypoxia and hypercapnic acidosis were induced by

gassing the solution with 12% CO_2, 88% N_2. Suffusate was pumped at 30 ml/min into the bath chamber (volume of 3 ml), which was thermoregulated to 37 ± 0.5°C. After electrodes were in place the bath was covered partially with Parafilm M to reduce contamination by room air. Samples were collected anaerobically from the center floor of the bath and were analyzed (Corning 165/2 blood gas analyzer) for pH and oxygen tension.

For a given experiment each pair of adult and neonatal nodal tissues was exposed, after a 30 min control drug free period, to stepwise, increasing concentrations of either lidocaine (0.05–0.8 mM, or 12–180 μg/ml) or bupivacaine (0.01–0.4 mM, or 3–120 μg/ml) during conditions of normoxia and isocarbia. The sequence was then repeated during conditions of hypoxia and acidosis. Nodal rates were recorded 10 min after each change in concentration when rates had stabilized. Absolute pacemaker rates and the percentage change from the control (normoxia, drug free) for each pair of adult and neonatal tissues were summarized statistically using two-way analysis of variance and subsequent comparison of means testing. Linear regression slope analysis and slope homogeneity testing were used to compare the percentage change of adult rates against neonatal rates as a function of lidocaine or bupivacaine during the control normoxic condition. Slope comparisons were similarly made during the hypoxic, acidotic condition. A P value of 0.05 or smaller indicated statistical significance. All values were summarized by the mean ± SEM.

Results
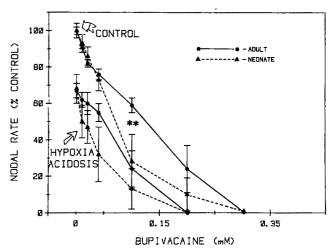
Control nodal rates in the lidocaine group were significantly slower (P < 0.001) in the adult (253 ± 7 beats/min) than in the neonatal (310 ± 5 beats/min) group. Control rates in the bupivacaine group were similarly slower in adults (229 ± 4 beats/min) than in neonates (295 ± 11 beats/min). During normoxia (pH 7.40 ± 0.01, Po₂ 482 ± 12 torr) the percentage decrease in neonatal rate was increasingly greater than the percentage decrease in adult rate with increasing concentrations of lidocaine (Fig. 1). For adult nodes during normoxia the correlation coefficient (r^2) was −0.92, the slope (m) was −90 and the y intercept (b) was 98%; for neonatal nodes during normoxia r^2 was −0.87, m was −182 and b was 101%. For both treatment groups, hypoxia and acidosis (pH 7.01 ± 0.03, Po₂ 58 ± 5 torr) alone significantly lowered adult rates by 73 ± 4 beats/min (P < 0.001) and neonatal rates by 84 ± 5 beats/min (P < 0.001) compared to the normoxic control rates. During hypoxia and acidosis, the percentage decrease in neonatal rates with 0.4 mM

Figure 1. The slowing effects of lidocaine and hypoxia with acidosis on pacemaker rates of paired ($n = 11$) adult and neonatal sinoatrial nodes as a percentage of their respective control rates during normoxic, drug free conditions. *** $= P < 0.001$, ** $= P < 0.01$, * $= P < 0.05$. See text for details.

Figure 2. The slowing effects of bupivacaine and hypoxia with acidosis on pacemaker rates of paired ($n = 4$) adult and neonatal sinoatrial nodes as a percentage of their respective control rates during normoxic, drug free conditions. ** $= P < 0.05$. See text for details.

lidocaine was greater than in adults ($P < 0.01$). Regression of the percentage change in nodal rates during hypoxia and acidosis as a function of lidocaine for adults gave these results: $r^2 = -0.82$, $m = -165$, and $b = 71\%$; for neonates $r^2 = -0.87$, $m = -257$, and $b = 74\%$. With a suffusion of 0.4 mM lidocaine, action potentials could not be detected during normoxia in five neonatal nodes, and during hypoxia and acidosis, in two adult nodes or in any of the neonatal nodes; during normoxia with 0.8 mM lidocaine action potentials were abolished in all neonatal nodes but in none of the adult nodes. Although hypoxia with acidosis caused a significant decrease in the y intercepts of both age groups, there were no significant differences in the adult or in the neonatal rate–lidocaine slopes between the control and the hypoxic, acidotic conditions.

Figure 2 shows the effect of bupivacaine on sinoatrial nodal rates. Compared with lidocaine (Fig. 1), equimolar concentrations of bupivacaine were about 4–5 times more potent in depressing adult and neonatal rates. At a concentration of 0.1 mM bupivacaine during normoxia the percentage decrease in rate in the neonate was greater than in the adult ($P < 0.05$). There was no significant difference between the slopes of adult and neonatal rates during either the control (normoxia) or the hypoxic, acidotic condition. During normoxia 0.2 mM bupivacaine arrested sinoatrial activity in half of the adult nodes and in all but one of the neonatal nodes; there were no detectable action potentials or changes in membrane potential at 0.3 mM bupivacaine. During hypoxia and acidosis, two adult nodes and one neonatal node continued to ex-

hibit electrical activity at 0.1 mM bupivacaine; there was no activity in any nodal tissue at 0.2 mM bupivacaine.

Figure 3 shows the overall effect of 0.4 mM lidocaine on the action potential of the adult sinoatrial node. Figure 4 details the change in phase 4 and phase 0 depolarizations with lidocaine. Table 1 summarizes the changes in action potential characteristics with 0.4 mM lidocaine. Changes in action potential properties of adults and neonates were not rigorously evaluated, but qualitatively similar changes (i.e., decreased phase 4 and phase 0 depolarization slopes and increased action potential duration) were observed with increasing concentrations of either local anesthetic.

Discussion

We have observed the following: 1) Increasing concentrations of lidocaine produced a rate of decrease in neonatal sinoatrial rates nearly twice that produced in adult nodes after normalizing for the faster intrinsic control rates of the neonatal nodes. 2) Although bupivacaine could not be shown to depress neonatal rates more than adult rates at all concentrations, the higher concentrations of bupivacaine were more effective in abolishing pacemaker activity than were the higher concentrations of lidocaine. 3) Bupivacaine was 4–5 times more potent than lidocaine in directly depressing pacemaker activity of adult and neonatal nodes. 4) The depression of nodal activity by increasing concentrations of either lidocaine or bupivacaine during hypoxia and acidosis was additive to the depression produced during normoxia.

CONTROL

**LIDOCAINE
.4 mM**

40
mV

400ms   100ms
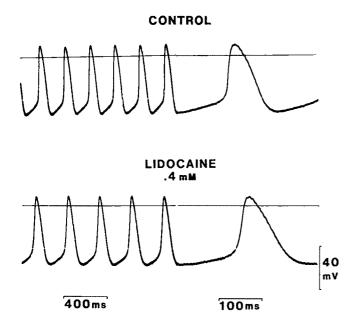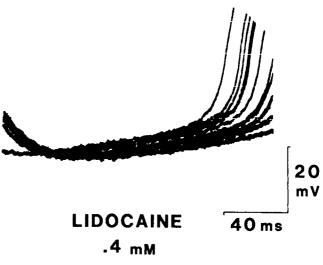
Figure 3. Spontaneous transmembrane action potentials recorded from an adult sinoatrial node during suffusion with oxygenated Krebs-Ringer solution in the presence and absence (control) of 0.4 mM lidocaine. The control rate is 280 beats/min; with lidocaine the rate is 208 beats/min.

20
mV

LIDOCAINE   40 ms
.4 mM

Figure 4. Depression of phase 4 (flatter curves) and phase 0 (up-stroke curves) depolarization slopes with lidocaine in the adult sinoatrial node during normoxia. Superimposed and successive tracings show rapidly decreasing phase 4 slopes and delayed and decreasing phase 0 slopes with exposure to lidocaine, which slows the pacemaker rate.

The comparative cardiovascular toxic effects of supratherapeutic doses of lidocaine and bupivacaine have been extensively studied. Cardiac arrest preceded by convulsions has occurred after regional anesthesia with bupivacaine in humans (1,3–5). The threshold blood level of bupivacaine that produces seizures and cardiovascular collapse after intravenous injection in humans is estimated to be as low as 3–6 μg/ml (3). A recent study in sheep (9) showed that the ratio of blood concentrations at which convulsions vs cardiovascular collapse first occurred was half as much for bupivacaine as it was for lidocaine; mean concentrations of 5 μg/ml bupivacaine and 40 μg/ml lidocaine caused circulatory collapse. In another study, peak blood levels of 70 μg/ml lidocaine following intravenous injection in awake sheep have caused only mild reflex tachycardia and ST segment T wave changes, whereas peak blood levels of 10 μg/ml bupivacaine caused serious dysrhythmias such as supraventricular tachycardia, atrioventricular block, ventricular tachycardia, premature ventricular excitations, and wide QRS complexes despite near normal arterial oxygen tension and pH (21). In ventilated cats subconvulsant doses of bupivacaine, but not lidocaine, precipitate nodal and ventricular dysrhythmias (10). Other cardiotoxic effects of bupivacaine, described in intact dogs with blood concentrations greater than 2 μg/ml, include increased conduction time across atria and prolonged atrioventricular nodal refractory period, de-

creased left ventricular contractility, and increased QRS width (11). In apneic dogs ventricular tachycardia and electromechanical dissociation are produced with bupivacaine overdosage (12). In an isolated rat heart preparation bupivacaine is six times more potent in decreasing the atrial rate, 14 times more potent in decreasing the ventricular rate, and 17 times more potent than lidocaine in increasing the PR interval (13). In the isolated, perfused guinea pig heart a suffusate concentration of 3 μg/ml of bupivacaine causes greater decreases in heart rate, the rate of force development, coronary blood flow and oxygen consumption than 10 μg/ml lidocaine (15). In isolated guinea pig atria bupivacaine is ten times more effective than lidocaine in decreasing muscle contractures by 50% and 6 times more effective in decreasing the atrial rate by 50% (14).

Electrophysiologic studies suggest that local anesthetics are more potent in producing conduction block than in depressing the pacing rate. In an older study of isolated suffused rabbit heart tissue, it was reported that up to 20 μg/ml lidocaine produced no slowing of the spontaneous sinoatrial nodal pacemaker, but that only 8–10 μg/ml were necessary to produce sinoatrial block and slow the atrial rate (22). Our study offers new evidence that bupivacaine is 4–5 times more potent than is lidocaine in directly depressing sinoatrial pacemaker activity, which is similar to the relative anesthetic potencies of bupivacaine to lidocaine (4:1) in blocking nerve conduction. Our study also supports an early electrophysiologic

Table 1. Summary of Effects of 0.4 mM Lidocaine on Transmembrane Action Potentials of Adult Sinoatrial Nodes

	Control	0.4 mM Lidocaine
Phase 4	123 ± 14 mV/s	77 ± 24 mV/s
Phase 0	2.9 ± 0.3 V/s	1.5 ± 0.3 V/s
ADP 50[a]	71 ± 1 ms	108 ± 17 ms

[a]APD 50, action potential duration at 50% of the maximal action potential amplitude.

study (23) that showed that suffusate concentrations of lidocaine greater than 23 μg/ml were necessary to depress the sinoatrial rate and the slope of phase 0 depolarization; that study also reported that this concentration of lidocaine decreased the amplitude of the action potential and the rate of phase 0 depolarization in atrial fibers.

We attempted to determine if the suffusate concentrations that slowed pacemaker activity in our in vitro study are within the threshold dose range for producing cardiotoxicity in humans. Assuming bupivacaine and lidocaine blood/plasma concentration ratios of about 0.75 (8), and 75% binding of bupivacaine and 50% binding of lidocaine to plasma proteins at normal pH (24), the ratio of the concentration of bupivacaine in whole blood to that in a protein-free artificial suffusate is 3:1; for lidocaine, this ratio is 1.5:1. Using these approximations the range of 0.01–0.4 mM (3–120 μg/ml) bupivacaine in the suffusate solution at normal pH corresponds to 9–360 μg/ml bupivacaine in whole blood; for lidocaine the suffusate range of 0.05–0.8 mM (12–180 μg/ml) corresponds to 18–270 μg/ml in whole blood. Bupivacaine in doses of 200 mg has been associated with cardiotoxicity in humans (1). Using estimates of 0.7 μg/ml (25) to 5 μg/ml (26) peak blood concentrations for each mg/kg of bupivacaine injected, a 200 mg intravascular dose in a 70 kg individual would cause peak bupivacaine blood concentrations of 1.5 to 10.5 μg/ml. We found that suffusate levels of 3–6 μg/ml (Fig. 2) produced approximately a 10% decrease in adult and neonatal rates during control, but a 38% decrease in adult rates and a 50% decrease in neonatal rates during hypoxia and acidosis. As noted above for sheep, bupivacaine levels of 5–10 μg/ml produced severe dysrhythmias and cardiovascular collapse (9,21), whereas 40 μg/ml lidocaine was necessary to produce circulatory collapse (9).

In addition to comparing the effects of lidocaine and bupivacaine on sinoatrial activity, we examined the concomitant effect of hypoxia with acidosis because central nervous system toxicity and cardiotoxicity to local anesthetic agents in humans are often accompanied by hypoxemia and acidemia (1,2,3–5). In a recent report awake, unanesthetized sheep were made hypoxic and acidotic before injection of bupivacaine (2.1 mg/kg) or lidocaine (5.7 mg/kg); the incidence of severe dysrhythmias after injection of bupivacaine was found to be greater—and resuscitative efforts with correction of acidemia were found to be relatively unsuccessful—than after injection of lidocaine (27). In another recent study (16) the effects of lidocaine and bupivacaine on the rate and force of atrial contraction were compared in isolated guinea pig atrial tissue exposed to a hypercapnic, acidotic (pH 6.7, PCO_2 167 torr), and mildly hypoxic (PO_2 201 torr) solution. The authors observed that the combination of hypoxia and acidosis enhanced the depression of the atrial contraction rate caused by 10 μg/ml bupivacaine in the perfusate from 62% to 94% of control; but neither hypoxia nor acidosis alone affected the decrease in atrial rate from control rates caused by bupivacaine. They also noted that a 34% decrease in atrial rate with 50 μg/ml lidocaine during control was unaffected by hypoxia and acidosis. Our results demonstrate that hypercapnic acidosis (pH 7.01) with a much lower level of hypoxia (PO_2 of 58 torr) directly depresses the sinoatrial pacemaker center in both neonates and adults, and that the slowing of rates produced by hypoxia with acidosis is additive to that produced by lidocaine and bupivacaine. Lower concentrations of local anesthetic agents are more likely to produce atrial conduction block than to cause sinoatrial nodal slowing (22). We have previously reported that the combination of severe hypoxia and acidosis results in a greater decrease in sinoatrial nodal pacemaker rate in the neonate than in the adult (20).

A major purpose of our study was to determine if the neonatal cardiac pacemaker is more or less sensitive to local anesthetic agents than is the adult pacemaker. Based on a comparison of slopes, we found that the percentage decrease in neonatal rates with increasing concentrations of lidocaine was about twice that of adult rates during either normoxic or hypoxic and acidotic conditions. The incidence of cessation of impulse formation was greater for bupivacaine than for lidocaine at the higher concentrations of each agent. Our findings may have a clinical correlate because fetal heart rate slowing has been observed in 20–30% of human parturients after paracervical block with bupivacaine (8). The incidence of late decelerations is threefold to fivefold greater with 0.5% bupivacaine than with 1.5% lidocaine epidural anesthesia administered by bolus injection (6) or bolus injection followed by continuous infusion (7). However, the fetal and neonatal lamb are more resistant to cardiovascular collapse induced by lidocaine than adult sheep

at the same tissue level of lidocaine (28). The steady state fetal blood concentration of bupivacaine is about one third that of the maternal blood; for lidocaine it is about one half (18). But fetal protein binding of local anesthetics is about 50% that of adults (8), which may increase the fetal (and neonatal) free drug concentration responsible for toxicity. Moreover, the lower fetal/maternal bupivacaine concentration ratio may be due to increased fetal tissue uptake rather than to decreased placental transfer (18).

The mechanism by which bupivacaine depresses the cardiac pacemaker rate at concentrations 4–5 times less than those of lidocaine was not directly examined in these experiments. We have observed only that the phase 0 and phase 4 action potential upstrokes decline, the action potential amplitude diminishes, and the action potential duration increases as the interval between action potentials increases with either agent. In ventricular myocytes sodium channels are blocked by local anesthetic agents in the relatively depolarized active (phase 0 upstroke) and inactive (phase 3 plateau) states (29). Lidocaine, a smaller and less lipid-soluble molecule than bupivacaine, rapidly blocks sodium channels in both the active and inactive states; however, lidocaine has been shown to bind only loosely, it is rapidly unbound, and it is less dependent on the frequency of depolarization (29). In a recent study bupivacaine, which also has been shown to block sodium channels in the active state, appeared to block sodium channels in the inactive (plateau) state much more avidly than did lidocaine (30). Because bupivacaine is so tightly bound, the half-life for recovery from block during the resting (polarized) state is much longer. The authors (30), using the maximal rate of phase 0 depolarization of guinea pig ventricular cells as an index of sodium channel binding, furnished evidence that at normal heart rates the channel block by bupivacaine can accumulate; this may explain the greater occurrence of cardiac conduction blockade and the higher potential for severe dysrhythmias with doses of bupivacaine that are comparable to doses of lidocaine producing neurotoxicity. It is possible that our observation of a greater effect of bupivacaine than of lidocaine on slowing the sinoatrial nodal rate is due to its greater affinity for, and slower dissociation from, nodal sodium channels during the "slow" action potential of pacemaker cells.

In conclusion, we have shown that bupivacaine is more potent than lidocaine in depressing and abolishing intrinsic sinoatrial node activity in vitro, and that the depressant effect of these agents is additively enhanced by hypoxia and acidosis. Moreover, the in vitro neonatal node is more sensitive than the in vitro adult node to a slowing and cessation of pacemaker

activity with increasing concentrations of lidocaine and bupivacaine. Although the effects of local anesthetic agents on the sinoatrial node may not be as deleterious as their effects on blocking impulse conduction and producing ventricular dysrhythmias, the greater potential for inhibition of intrinsic pacemaker activity by bupivacaine, especially in the hypoxic, acidotic fetus during parturition, must be considered to avoid possible serious bradyarrhythmias and other cardiotoxic effects during regional anesthesia with bupivacaine.

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Plasma Diltiazem Levels, Cardiovascular Function, and Coronary Hemodynamics during Enflurane Anesthesia in the Dog

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KAPUR PA, CAMPOS JH, BUCHEA OC. Plasma diltiazem levels, cardiovascular function, and coronary hemodynamics during enflurane anesthesia in the dog. Anesth Analg 1986;65:918–24.

Diltiazem was administered to dogs by an intravenous infusion protocol, which resulted in plasma levels of 71 ± 6 (n = 7), 139 ± 9 (n = 7), 353 ± 33 (n = 10), and 1064 ± 143 (n = 6) ng/ml, to evaluate the effects of diltiazem on cardiovascular function and coronary hemodynamics in the presence of anesthetic concentrations of enflurane. An additional group of six dogs received enflurane only. The only changes observed with enflurane alone were a decrease in left ventricular (LV) dP/dt, cardiac index (CI), and coronary blood flow 60 min after the baseline measurements were made. In all of the diltiazem groups, plasma level-related prolongation of the PR interval of the electrocardiogram was observed, with development of second degree heart block and junctional rhythms in animals at the two higher plasma levels. Mean arterial pressure and LV dP/dt decreased at the two higher diltiazem plasma levels after 30 min of infusion, and three of six dogs in the highest group had to be dropped from the study because of severe hypotension. The cardiac index was no different from enflurane alone with the three lower plasma diltiazem levels. No changes were observed in coronary sinus blood flow, coronary vascular resistance, myocardial oxygen uptake, or myocardial lactate extraction. Circulating norepinephrine levels were elevated in the two higher diltiazem groups. In the presence of anesthetic concentrations of enflurane, over the range of plasma diltiazem levels investigated in this study, conduction effects were prominent and decreases in left ventricular performance and blood pressure occurred as plasma diltiazem levels increased. No untoward effects on global myocardial metabolism were detected at plasma levels less than 500 ng/ml. However, the occurrence of circulatory collapse in half of the animals at the highest plasma levels prevented evaluation of metabolic effects of high levels of diltiazem during enflurane anesthesia.

Key Words: ANESTHETICS, VOLATILE—enflurane. HEART—coronary blood flow, myocardial function. IONS—calcium. PHARMACOLOGY—diltiazem.

Diltiazem has a spectrum of clinical usefulness similar to that of verapamil (1–6). Because combined cardiovascular depressant effects may limit the use of verapamil in the presence of inhalation anesthestics (7), diltiazem may be a potential alternative if therapeutically indicated during inhalation anesthesia. Previous work in our laboratory has demonstrated that clinically relevant plasma levels of diltiazem are generally well-tolerated during 1.5% end-tidal isoflurane anesthesia in a canine model (8). Plasma level-related prolongation of the PR interval of the electrocardiogram and mild depression of left ventricular dP/dt were the major findings. No alterations in global left ventricular oxygen consumption or coronary hemodynamics were noted. However, the previous study was limited to isoflurane and to plasma levels of dil-

tiazem less than 600 ng/ml. Diltiazem may not be as well-tolerated by the heart in combination with a different anesthetic, such as enflurane. Other investigations have shown that the decreased blood pressure observed with clinical concentrations of enflurane is associated with a decrease in cardiac output, as compared to the marked decrease in peripheral vascular resistance associated with decreased blood pressure in the presence of clinical concentrations of isoflurane (9,10).

The present study was therefore undertaken to achieve a range of plasma levels of diltiazem during enflurane anesthesia in an instrumented canine model to evaluate the plasma level-related effects of diltiazem on cardiovascular function and coronary hemodynamics in the presence of anesthetic concentrations of enflurane.

Methods

Nineteen conditioned mongrel dogs of either sex weighing 23 ± 1 kg (mean ± SEM) with chronic tra-

cheostomies (11) to facilitate an inhalation anesthetic induction were used for the experiments. Anesthesia consisted of enflurane (2.2–2.4% end tidal concentration) in 40% oxygen in air through a cuffed tracheostomy tube. Ventilation was controlled to maintain normocarbia. Temperature was maintained between 38–39°C with a warming blanket and a heat lamp. The experimental preparation was identical to that in a previous study with isoflurane (8). Catheters were placed in an external jugular vein for drug administration and infusion of 0.9% NaCl at 5 ml·kg^{-1}·hr^{-1}, in a femoral artery for blood samples and measurement of phasic and mean arterial blood pressure (MAP), and in a pulmonary artery for measurement of right atrial (RA) and pulmonary artery occluded (PAO) pressures and for sampling of mixed venous blood. A micromanometer-tipped catheter (Millar Instruments, Inc., Houston, Texas) was positioned in the left ventricle from a femoral artery for measurement of left ventricular (LV) pressure and electronic derivation of LV dP/dt. A 7F woven Dacron coronary sinus thermodilution catheter (Model CCS-7U-90B, Webster Laboratories, Inc., Altadena, California) was passed into the coronary sinus under fluoroscopic control via an external jugular vein to measure coronary sinus (CS) pressures and blood flow and to obtain CS blood samples. Its position was confirmed every 30 min as in the prior study (8). Coronary sinus blood flow (Q̇cs) was measured in duplicate by means of a technique adapted from Ganz et al. (12), as detailed previously (8).

Heart rate (HR), MAP, RA, PA, CS, and LV pressures, and LV dP/dt were continuously recorded. In addition the ECG was intermittently recorded at fast paper speed (100 mm/s) for measurement of PR intervals. Inhaled and exhaled gases were analyzed by a mass spectrometer and exhaled gas volume was measured with a modified electronic volume displacement spirometer (8). Intermittent samples were simultaneously taken of arterial, mixed venous, and CS blood for blood gas tensions, pH, and blood oxygen content. Cardiac output was determined by the Fick method. Systemic vascular resistance (SVR), coronary vascular resistance (CVR), cardiac index (CI), whole body oxygen uptake (V̇O$_2$), and myocardial oxygen uptake (MV̇O$_2$) were calculated (8).

Plasma arterial diltiazem and arterial and CS catecholamine levels were assayed by high performance liquid chromatography (13,14). Plasma lactate levels were assayed by a method adapted from Marbach and Weil (15). Myocardial lactate extraction ratio (MLE) was calculated as the product of arterial lactate levels minus CS lactate levels, divided by the arterial lactate level, and multiplied by 100. Serum levels of electro-

lytes (Na$^+$, K$^+$, Cl$^-$), glucose, and ionized calcium were measured using an automated analyzer (Beckman Instruments).

In six dogs enflurane anesthesia was continued with cardiovascular measurements and plasma samples repeated every 30 min (group E). For the other 15 experiments in 13 dogs, diltiazem was freshly prepared in 0.9% NaCl to a concentration of 0.5 mg/ml. To produce a range of plasma diltiazem levels, four intravenous loading dose and infusion combinations were chosen: A, 100 μg/kg + 4 μg·kg^{-1}·min^{-1}; B, 200 μg/kg + 8 μg·kg^{-1}·min^{-1}; C, 300 μg/kg + 12 μg·kg^{-1}·min^{-1}; D, 400 μg/kg + 20 μg·kg^{-1}·min^{-1}. After a 2 hr stabilization under enflurane anesthesia, baseline blood samples and hemodynamic measurements were made. Each experiment then consisted of either dose A followed by dose D (n = 7), or dose B followed by dose C (n = 8). The loading dose was given over 5 min and the infusion continued for 30 min, at which time the second loading dose was given in a like manner and the infusion rate increased. Differences in drug disposition among the animals were anticipated, and it was planned that the experimental results would be analyzed not as a function of dose, but as a function of plasma diltiazem level. The two dogs that were studied twice received the alternate pair of diltiazem doses during the second experiment, which was separated from the first by at least 3 weeks.

Cardiovascular measurements and samples for measurement of plasma levels of diltiazem, epinephrine, and norepinephrine were taken at 20 and 30 min of each infusion. The 30 min values from the first infusion rate served as control measurements for the second infusion. Measurements were also made 90 min after stopping the second infusion in each experiment. The study was discontinued if mean arterial pressure decreased below 50 mm Hg.

Analysis of variance and analysis of variance for repeated measures with Bonferroni t-tests were used to evaluate the statistical significance of the data. A nonpaired t-test was used to compare the end of infusion values for group III with the 60 min values for group E because the small number of animals (three) completing group IV precluded comparative analysis of that group.

Results

Normal levels of arterial pH, PaO$_2$, PaCO$_2$, hematocrit, and temperature were maintained throughout the study. There were no significant changes in serum levels of electrolytes, ionized calcium, or glucose. Overlap of plasma diltiazem levels did occur among the infusion rates for different animals receiving dil-

Table 1. Cardiovascular Measures for Animals Receiving Enflurane Alone (E) and Those Receiving Diltiazem (I–IV)[a]

	Group	n	Control	30 min[b]	60 min
HR (bpm)	E	6	128 ± 7	128 ± 7	125 ± 7
	I	7	133 ± 3	122 ± 3[c]	—
	II	7	136 ± 4	113 ± 6[c]	—
	III	10	—	122 ± 4	110 ± 5[c,f]
	IV	6	—	115 ± 6	—[e]
MAP (mm Hg)	E	6	85 ± 5	85 ± 4	87 ± 3
	I	7	91 ± 4	85 ± 2	—
	II	7	87 ± 3	83 ± 7	—
	III	10	—	87 ± 4	70 ± 3[c,d]
	IV	6	—	77 ± 7	56 ± 6[e]
PAO pressure (mm Hg)	E	6	9 ± 1	8 ± 1	6 ± 1
	I	7	7 ± 1	6 ± 1	—
	II	7	8 ± 1	8 ± 1	—
	III	10	—	7 ± 1	9 ± 1[c]
	IV	6	—	8 ± 1	15 ± 2[e]
RA pressure (mm Hg)	E	6	5 ± 1	4 ± 1	4 ± 1
	I	7	3 ± 1	3 ± 1	—
	II	7	4 ± 1	5 ± 1	—
	III	10	—	4 ± 1	7 ± 1[c]
	IV	6	—	5 ± 1	9 ± 2[e]
LV dP/dt (mm Hg/s)	E	6	1915 ± 228	1775 ± 219	1620 ± 187[c]
	I	7	1903 ± 129	1611 ± 109[c]	—
	II	6	1897 ± 220	1517 ± 178[c]	—
	III	9	—	1550 ± 120	1048 ± 104[c,d]
	IV	6	—	1345 ± 212	1133 ± 260[e]
CI (L·min⁻¹·m⁻²)	E	6	6.39 ± 1.24	4.82 ± 0.95	3.60 ± 0.47[c]
	I	7	7.03 ± 1.21	4.88 ± 0.45	—
	II	7	4.89 ± 0.73	4.02 ± 0.49	—
	III	10	—	4.63 ± 0.34	3.34 ± 0.47[c]
	IV	6	—	3.52 ± 0.68	2.16 ± 0.74[e]
SVR (dynes·s·cm⁻⁵)	E	6	1580 ± 521	1978 ± 476	2341 ± 298
	I	7	1180 ± 145	1496 ± 157	—
	II	7	1561 ± 174	1343 ± 157	—
	III	10	—	1632 ± 151	1859 ± 173
	IV	6	—	1729 ± 154	1796 ± 298[e]
PR interval (ms)	E	6	105 ± 4	107 ± 4	105 ± 3
	I	7	116 ± 7	128 ± 7[c]	—
	II	7	117 ± 9	151 ± 17[c,d]	—
	III	10		135 ± 13	164 ± 7[c,d,f]
	IV	6		145 ± 10[d]	—[e]
Diltiazem (ng/ml)	C	6	—	—	—
	I	7	—	71 ± 6	—
	II	7	—	139 ± 9	—
	III	10	—	106 ± 15	353 ± 33
	IV	6	—	144 ± 42	887 ± 179[e]

Abbreviations: HR, heart rate; PAO, pulmonary artery occluded; RA, right atrial; LV, left ventricular; CI, cardiac index; SVR, systemic vascular resistance.
[a]All values are mean ± SEM.
[b]Values at 30 min are "control" values for groups III and IV.
[c]$P < 0.05$ compared to control for groups E, I, II, or to 30 min "control" values for groups III and IV.
[d]$P < 0.05$ compared to group E at the same measurement time.
[e]Values shown for animals completing the study, $n = 3$.
[f]$n = 8$; 2/10 animals in group III developed Wenckebach second degree heart block.

Table 2. Coronary and Myocardial Metabolic Measures for Animals Receiving Enflurane Alone (E) and Those Also Receiving Diltiazem (I–IV)

	Group	n	Control	30 min[a]	60 min
$\dot{Q}cs$ (ml·min^{-1})	E	6	114 ± 22	85 ± 24	70 ± 23[b]
	I	6	99 ± 12	72 ± 11	—
	II	7	84 ± 5	80 ± 10	—
	III	8	—	79 ± 3	59 ± 7
	IV	6	—	68 ± 33	57 ± 9[d]
CVR (mm Hg·ml^{-1}·min^{-1})	E	6	0.62 ± 0.13	0.79 ± 0.15	1.02 ± 0.13
	I	6	0.79 ± 0.11	0.99 ± 0.19	—
	II	6	0.79 ± 0.08	0.76 ± 0.11	—
	III	8	—	0.91 ± 0.16	0.84 ± 0.09
	IV	6	—	0.75 ± 0.17	0.75 ± 0.17[d]
MLE (%)	E	6	38.5 ± 5.3	41.3 ± 4.8	43.5 ± 5.4
	I	6	42.9 ± 3.9	36.8 ± 3.7	—
	II	6	45.6 ± 3.3	44.7 ± 2.2	—
	III	7	—	39.6 ± 2.4	40.3 ± 2.6
	IV	6	—	42.1 ± 4.0	39.3 ± 10.3[d]
$\dot{M}\text{V}o_2$ (ml/min)	E	6	8.11 ± 1.16	6.93 ± 0.86	6.17 ± 0.75
	I	6	8.77 ± 1.45	6.11 ± 0.88	—
	II	7	8.68 ± 0.54	8.31 ± 0.74	—
	III	8	—	6.98 ± 0.90	6.19 ± 0.76
	IV	6	—	7.84 ± 0.64	7.74 ± 1.73[d]
$\dot{V}o_2$ (ml/min)	E	6	117 ± 10	113 ± 9	110 ± 8
	I	7	165 ± 17	139 ± 8	—
	II	7	141 ± 9	149 ± 12	—
	III	10	—	132 ± 7	136 ± 7[c]
	IV	6	—	155 ± 12	194 ± 33[d]

Abbreviations: $\dot{Q}cs$, coronary sinus blood flow; CVR, coronary vascular resistance; MLE, myocardial lactate extraction; $\dot{M}\text{V}o_2$, myocardial oxygen consumption; $\dot{V}o_2$ total body oxygen consumption. All values are mean ± SEM.
[a]"Control" values for groups III and IV.
[b]$P < 0.05$ compared to the respective control value ("30 min" for groups III and IV).
[c]$P < 0.05$ compared to group E at the same measurement time.
[d]Values shown for animals completing the study; $n = 3$.

tiazem. Results for the diltiazem experiments were therefore sorted into four groups by the plasma diltiazem levels achieved at 30 min of each drug infusion rate: group I, 48–97 (71 ± 6) ng/ml ($n = 7$); group II, 114–152 (139 ± 9) ng/ml ($n = 7$); group III, 225–500 (353 ± 33) ng/ml ($n = 10$); and group IV, 716–1665 (1064 ± 143) ng/ml (n = 6). There were no statistically significant differences in the mean 20- and 30-min values during the infusions for any of the variables in any of the four diltiazem groups. Therefore, 30-min values are used in the tables. Three of the six animals with the highest diltiazem levels (group IV) were unable to complete the study because of hypotension. The mean plasma diltiazem level of the three group IV dogs completing the study was 887 ± 179 ng/ml.

Table 1 shows the values for hemodynamic variables for group E and for each of the four plasma diltiazem levels using the values at the end of each 30-min infusion. There were no differences among the values for groups E, I, and II at control. The only

changes observed in group E (enflurane only) over the time course of the experiment were a decrease in LV dP/dt, CI, and $\dot{Q}cs$, which occurred 60 min after the control measurements, the time comparable to 30 min of infusion of diltiazem at rates that gave higher plasma levels.

All four diltiazem infusion rates prolonged the PR interval of the ECG compared to the respective baseline measurements. Arterial diltiazem levels of approximately 140 ng/ml (see Table 1), found after 30 min of infusion in group II and as the control value for group IV, were associated with significant prolongation of the PR interval compared to group E at 30 min. Values for LV dP/dt in groups I and II were reduced at 30 min of infusion compared to their respective baseline values, but were not significantly decreased compared to group E at the similar time.

When end of infusion values for group III (diltiazem levels of 353 ± 33 ng/ml) were compared to their respective baseline values, significant decreases were found in HR, MAP, and LV dP/dt, with increases

Table 3. Plasma Epinephrine and Norepinephrine Levels in Arterial and Coronary Sinus (CS) Blood[a]

	Group	n	Control	30 min[b]	60 min
Arterial epinephrine (pg/ml)	E	6	357 ± 112	251 ± 52	213 ± 52
	I	7	153 ± 56	150 ± 53	—
	II	7	272 ± 81	375 ± 92	—
	III	10	—	229 ± 77	571 ± 239
	IV	6	—	266 ± 75	601 ± 216[e]
CS epinephrine (pg/ml)	E	6	102 ± 50	53 ± 12	39 ± 7
	I	6	30 ± 5	39 ± 10	—
	II	6	83 ± 27	79 ± 28	—
	III	8	—	51 ± 23	68 ± 27
	IV	6	—	52 ± 12	125 ± 26[e]
Arterial norepinephrine (pg/ml)	E	6	58 ± 17	45 ± 10	42 ± 9
	I	7	67 ± 14	68 ± 15	—
	II	7	64 ± 9	75 ± 13	—
	III	10	—	70 ± 13	157 ± 34[c,d]
	IV	6	—	70 ± 7	386 ± 175[e]
CS norepinephrine (pg/ml)	E	6	39 ± 12	28 ± 5	39 ± 12
	I	6	42 ± 8	57 ± 18	—
	II	6	33 ± 5	41 ± 8	—
	III	8	—	37 ± 7	58 ± 11[c]
	IV	6	—	55 ± 17	217 ± 90[e]

[a]All values are mean ± SEM.
[b]"Control" values for groups III and IV.
[c]$P < 0.05$ compared to the respective control value ("30 min" value for groups III and IV).
[d]$P < 0.05$ compared to group E at the same measurement time.
• [e]Values shown for animals completing the study; $n = 3$.

in PAO, RA, and PR interval. When group III was compared to group E at the appropriate time (60 min), MAP and LV dP/dt were decreased and PR interval increased. Statistical analysis of the effects of the highest levels of diltiazem (group IV) was impossible because of the small number of animals in group IV able to tolerate such high levels of diltiazem in the presence of 2.2–2.4% end tidal concentrations of enflurane. Abnormalities of atrioventricular conduction developed in two of the ten animals in group III (one junctional rhythm and one Wenckebach heart block) and five of six animals in group IV (four with junctional rhythms and one with Wenckebach heart block).

Coronary and metabolic measures for the five groups are shown in Table 2. Values for $\dot{Q}cs$, CVR, MLE, $M\dot{V}O_2$, and $\dot{V}O_2$ were not significantly different among the comparable groups at each time period, nor were there differences from the respective control values (30 min values are the "control" values for groups III and IV), with the exception of the decrease in $\dot{Q}cs$ that developed with time in the E group as previously noted. The baseline values for group IV were included to show that before the initiation of the higher infusion rate, the condition of those animals was not significantly different from the other groups.

Arterial and CS plasma levels of epinephrine and norepinephrine are shown in a similar format in Table 3. Norepinephrine levels were increased in group III

animals and although the number of group IV animals completing the study was small, the trend for increased norepinephrine at higher plasma diltiazem levels is apparent. Several animals had very high catecholamine levels ($>10^3$ pg/ml).

Discussion

In addition to the testing of enflurane in a previously developed animal model of diltiazem–anesthetic drug interactions (8), the present study included an "anesthetic only" control group to evaluate the effects of exposure to the anesthetic alone on the preparation and tested higher plasma levels of diltiazem. The effects of plasma levels of diltiazem less than 200 ng/ml were limited to mild bradycardia and prolongation of atrioventricular conduction in the presence of enflurane. Plasma diltiazem levels of between 200–500 ng/ml were also associated with decreased MAP and LV dP/dt, and increased PAO and RA compared to predrug controls. At intermediate drug levels both MAP and LV dP/dt were depressed by diltiazem beyond the decrease that occurred from the time-related effects of enflurane. The cardiac index was reasonably well-preserved up to plasma diltiazem levels of 500 ng/ml. Global left ventricular coronary and myocardial metabolic measurements, as based upon the type of coronary sinus catheter used in the present

study, were similar in the presence of plasma levels of diltiazem less than 500 ng/ml as compared to enflurane alone, despite mild hemodynamic changes and measureable effects on intracardiac conduction in the diltiazem groups. In the present study with enflurane, plasma levels approximating 1000 ng/ml were not tolerated, as evidenced by the inability to maintain mean arterial pressure at or above 50 mm Hg. An unacceptable frequency of conduction abnormalities (5/6) was also associated with the highest diltiazem levels.

Blood pressure was decreased by diltiazem in a dose-dependent manner in the presence of enflurane, although higher plasma levels were required to reduce blood pressure than were required to interfere with atrioventricular conduction. Despite a reduction in several determinants of myocardial oxygen demand, such as HR, MAP, and LV dP/dt, myocardial oxygen consumption was not found to decrease. Perhaps this represents an inefficient oxygen utilization under the circumstances of the study.

Circulating catecholamine levels were only increased at plasma levels of diltiazem that were associated with significant decreases in blood pressure. In the highest plasma diltiazem level group, catecholamine levels were very high in the animals that were the most compromised. Apparently the levels of endogenous catecholamines that were achieved in the presence of the high diltiazem levels were frequently insufficient to compensate for the direct depressant effects of the diltiazem–enflurane combination. Heart rates were not elevated even with elevated catecholamine levels because five of the six animals in group IV were already in heart block. Perhaps the much higher levels of circulating catecholamines that can be achieved by exogenous administration would effectively reverse the depressant effects of high diltiazem levels with enflurane. We did not test this hypothesis because in the animals in which the study was aborted (upon reaching a MAP of 50 mm Hg), the hemodynamic profile was improved in every case by the administration of exogenous calcium chloride, as has been previously demonstrated by others (16).

The nature of the findings in the present study were similar to those for the lower diltiazem levels tested in the presence of isoflurane in the prior study (8), except that a decrease in blood pressure was not seen with plasma levels of diltiazem of less than 500 ng/ml in the animals anesthetized with isoflurane. The interpretation of these findings assumes that equipotent anesthetic concentrations were present for both inhalation agents in the present and prior studies. Although we have not performed MAC studies in these animals, our anesthetic concentrations closely approximate previously published values for the MAC

of enflurane and isoflurane in dogs (17,18). In the two studies, neither systemic nor coronary vasodilation was observed under the conditions of continuous diltiazem infusion at plasma diltiazem levels comparable to groups I–III with either inhalation anesthetic agent. Kates et al. similarly did not observe systemic vasodilation with continuous infusions of diltiazem during halothane anesthesia in swine (16).

Possible perioperative parenteral use of diltiazem could include not only the treatment of suitable arrhythmias or episodes of myocardial ischemia, but also a component of cardioplegia solutions (6,19). Although interpretation of specific plasma levels of drugs between species is difficult, similar plasma level-related pharmacodynamic phenomena are frequently observed, even if at slightly different plasma level thresholds. The plasma levels chosen in this study (groups I, II, III, and IV), represent approximately low, mid, high, and well above therapeutic levels in man. We have shown that at plasma levels of less than 200 ng/ml in this canine model, atrioventricular conduction may be prolonged with relatively benign hemodynamic effects. The lowered values of MAP and LV dP/dt at plasma levels of diltiazem above 200 ng/ml may perhaps indicate caution if rapid infusions or large amounts of diltiazem are to be administered in the presence of enflurane. To the extent that results from animal studies can be extrapolated to man, in the presence of anesthetic concentrations of enflurane, plasma diltiazem levels above 500 ng/ml may result in an unacceptable frequency of severe cardiovascular depression and intracardiac conduction impairment, despite increased circulating catecholamine levels.

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Cardiopulmonary Effects of Oleic Acid-Induced Pulmonary Edema and Mechanical Ventilation

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HENNING RJ, HEYMAN V, ALCOVER I, ROMEO S. Cardiopulmonary effects of oleic acid-induced pulmonary edema and mechanical ventilation. Anesth Analg 1986;65:925–32.

In order to define the mechanisms whereby cardiac output and arterial oxygen transport are reduced by acute permeability pulmonary edema and by positive end-expiratory pressure (PEEP), hemodynamic, respiratory, and lung water changes were measured in 12 mechanically ventilated dogs prior to the injection of oleic acid and at 1, 2.5, and 4 hr after the injection. Measurements were performed at each interval before and after the addition of 20 cm H₂O PEEP. Positive end-expiratory pressure was not continued between measurements. One hour after the oleic acid injection, the lung water content and the pulmonary vascular resistance had increased more than 100% while the right ventricular (RV) volume, RV stroke volume, and PaO₂ had decreased

more than 35%. Each application of PEEP increased the PaO₂ to control levels. However, PEEP also significantly increased the lung water content and pulmonary vascular resistance, and decreased the RV volume and stroke volume by 33%.

The extravasation of fluid from the intravascular to the interstitial and alveolar spaces of the lung with oleic acid pulmonary edema is associated with substantial decreases in right ventricular volume and stroke volume and significant increases in the pulmonary vascular resistance. Treatment with 20 cm H₂O PEEP further increases the lung water content and pulmonary vascular resistance and substantially reduces the right ventricular volume and stroke volume.

Key Words: LUNG—edema. VENTILATION—positive end-expiratory pressure.

Patients with acute pulmonary edema caused by increased permeability of the pulmonary capillary endothelium have severe dyspnea, hypoxia, increased lung water content, decreased pulmonary compliance, and normal cardiac filling pressures. The precise pathogenesis of acute permeability pulmonary edema is not known, but toxic or vasoactive substances, surfactant abnormalities, fat and white blood cell embolization, and lung ischemia have been implicated (1). Because of mismatched ventilation and perfusion with increased pulmonary shunt, increases in the inspired oxygen concentration have little or no effect on the arterial oxygen content. As the acute pulmonary edema progresses, significant depression of cardiac output often occurs, further compromising oxygen delivery to the tissues.

The use of positive pressure ventilation with positive end-expiratory pressure (PEEP) was initially de-

scribed by Cournand et al. in 1948 (2). Ashbaugh and Petty first recommended the use of PEEP for the treatment of acute permeability pulmonary edema in 1973 (3). However, the use of PEEP has been associated with an increased incidence of barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema) and a reduction in cardiac output that may also compromise oxygen delivery to the tissues.

The mechanisms whereby permeability pulmonary edema and mechanical ventilation with PEEP decrease cardiac output are controversial. Changes in pleural pressure, changes in right and left ventricular afterload, alterations in myocardial contractility, and reductions in ventricular preload have been postulated as possible mechanisms (3,4). We hypothesize that the decrease in cardiac output with acute permeability pulmonary edema is related to significant reductions in the plasma volume because of marked increases in lung water content. High levels of PEEP decrease the venous return to the right heart and further increase the lung water content. Therefore, in order to examine these hypotheses, serial hemodynamic and respiratory measurements were performed in dogs before and after the induction of oleic acid acute permeability pulmonary edema.

Materials and Methods

Twelve fasted, healthy, mongrel dogs, weighing between 18 and 26 kg, were anesthetized with 15 mg/kg of thiopental. Small supplemental doses of thiopental were given during the experiments to maintain surgical anesthesia as evidenced by the absence of eyelash and deep tendon reflexes. Each dog was artificially ventilated by a Harvard ventilator with a tidal volume of 15 ml/kg and given 60% inspired oxygen to maintain the hemoglobin fully saturated throughout the study. The tidal volume and ventilator frequency remained constant during the experiment. A 7 French pigtail catheter was passed into the left ventricle for measurements of left ventricular end-diastolic pressure. A thermistor catheter was placed in the left iliac artery to measure changes in core blood temperature and arterial blood pressure. A specially constructed balloon-tipped flotation catheter, containing a 120 ms response thermistor (Victory Engineering Company), was inserted through the right internal jugular vein. The catheter, which was guided by pressure monitoring into the pulmonary artery, enabled measurements of right atrial pressure, pulmonary artery and wedge pressures, cardiac output, and right ventricular volume and ejection fraction. Pressures were recorded with quartz pressure transducers, which were referenced to the level of the atria, and displayed on a thermal recorder (Hewlett Packard). The frequency response of the catheter–manometer systems was 30 c/sec. All pressures were measured at end-expiration over three respiratory cycles.

Right ventricular volumes were determined by thermodilution techniques (5–8). The balloon catheter contained a rapid response thermistor bead (2000 Ohm resistive load, 120 ms time constant). The thermistor bead enabled measurements of beat by beat changes in pulmonary artery blood temperature. Five to ten milliliters of chilled 5% dextrose in water was injected immediately above the tricuspid valve within two cardiac cycles. Beat-by-beat changes in the pulmonary artery blood temperature were obtained from a minimum of three sequential cardiac output curves. Measurements were initiated with the fourth beat after the end of the right atrial injection (9). Technically unsatisfactory curves were discarded.

The ratios of the end-diastolic washout temperature (T) plateaus, T_{n+1}/T_n, yielded the right ventricular residual fraction. A minimum of five ratio measurements that agreed within 10% were averaged to obtain the residual fraction measurements. The diastolic volume was determined from the stroke volume divided by one minus the residual fraction. The sys-

tolic volume was derived by subtracting the stroke volume from the diastolic volume.

The use of indicator solutions to measure ventricular volume and the formulas for volume determinations have been described by Holt (10). The technique has been validated in a physical analogue of the cardiac ventricle in which the heart rate, stroke volume, and end-diastolic volume have been controlled independently (7). Ventricular volumes measured by the thermodilution technique have been within 4 ml of immediate postmortem volume determinations at the same ventricular pressures (9). Right ventricular thermal measurements and radionucleotide measurements have correlated closely in dogs ($r = 0.86$) and also in patients with the adult respiratory distress syndrome ($r = 0.74$) (11,12).

Lung water and cardiac output were measured with the double indicator dilution technique with chilled indocyanine green dye injected via the right atrial port of the balloon catheter (13). The mean transit times of the thermal and green dye indicators between the right heart and the iliac artery were computed by a microprocessor (American Edwards). Three measurements that agreed within 10% were averaged to obtain the cardiac output and lung water measurements. The measurements of extravascular lung water by the thermal dye technique correlates ($r = 0.93$) with postmortem gravimetric lung water determinations (13). Stroke volume was computed by dividing the cardiac output by the heart rate. Pulmonary vascular resistance was calculated from the following formula: the mean pulmonary artery pressure minus left ventricular end-diastolic pressure divided by cardiac output times eighty. Because the oleic acid dog model of acute permeability pulmonary edema is a nonlinear system, pulmonary vascular resistance rather than pulmonary impedance was used as an index of right ventricular afterload (14).

Pleural pressures were measured with a thin-walled balloon, containing 0.8 ml of air, placed in the distal esophagus. The balloon was connected to a differential pressure transducer (Validyne Engineering Corporation, range $\pm$ 50 cm of water) via a polyethylene catheter (length 80 cm, internal diameter 1.7 mm). Over a range of balloon volumes of 0–2 ml, the balloon had a zero pressure. All dogs were placed in the left lateral decubitus or prone position to avoid potential problems with mediastinal compression of the esophagus and inaccurate pleural pressure measurements. Marini et al. have demonstrated that esophageal pressure measurements accurately reflect pleural pressure measurements when the dogs are placed in the prone or the lateral decubitus position (15). The pleural pressure measurements were sub-

tracted from right atrial, pulmonary artery, pulmonary wedge, and left ventricular end-diastolic pressure measurements to obtain transmural cardiac pressures.

Arterial blood samples were analyzed for Po_2, Pco_2, and hemoglobin concentration with a blood analyzer and spectrophotometer (Instrumentation Laboratories). The partial pressure gas measurements were corrected for body temperature. Two hundred fifty ml of hydroxyethyl starch (Hetastarch) was administered to all animals prior to the baseline measurements for plasma volume expansion. Additional hydroxyethyl starch was given to replace the urine output in each dog. Core temperature was monitored with the use of the central arterial thermistor catheter and was maintained at $37 \pm 1°C$ by the application of external heat lamps.
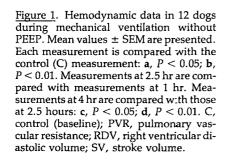
Control (baseline) measurements of pleural pressure, right atrial pressure, pulmonary artery and wedge pressure, left ventricular end-diastolic pressure, cardiac output, right ventricular volume, lung water, vascular resistance, hemoglobin concentration, and arterial gas tensions were performed in all dogs maintained on positive pressure ventilation. After the control measurements, 0.06 ml/kg of oleic acid was slowly injected into the right atrium for the induction of acute permeability pulmonary edema (16). All dogs were rotated from side to side and tilted in order to distribute the oleic acid throughout the lungs. Previous
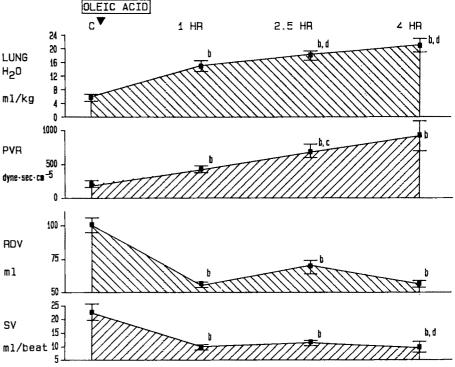
work in our laboratory has demonstrated that the dose of oleic acid used in the present study causes a 50% reduction in lung compliance within 4 hr. At 1, 2.5, and 4 hr after the oleic acid injection, all the hemodynamic, respiratory, and lung H_2O measurements were repeated before and after the gradual application of 20 cm H_2O PEEP. PEEP was created by submerging the expiratory tubing of the Harvard respirator to a depth of 20 cm below water. A minimum period of 10 min was allowed for equilibration after the addition of PEEP. Positive end-expiratory pressure was not maintained between the measurement periods. When the measurements were completed, the animals were killed by the intravenous injection of a saturated solution of potassium chloride. Autopsies were performed on all dogs.
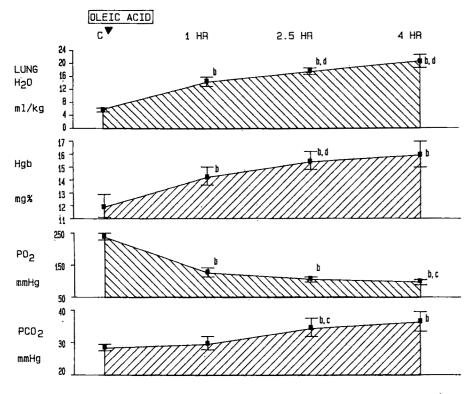
The data were analyzed by a mixed model analysis of variance (17). The fixed factors were time, oleic acid, and PEEP, and the random factor was the animals. Scheffe's test for paired observations was used to determine the level of statistical significance (18). A P value of <0.05 was considered statistically significant. Values presented are mean $\pm$ SEM.

Results

The hemodynamic and respiratory measurements for the twelve dogs during mechanical ventilation without PEEP are shown in Figures 1 and 2. With the

Figure 1. Hemodynamic data in 12 dogs during mechanical ventilation without PEEP. Mean values $\pm$ SEM are presented. Each measurement is compared with the control (C) measurement: a, $P < 0.05$; b, $P < 0.01$. Measurements at 2.5 hr are compared with measurements at 1 hr. Measurements at 4 hr are compared with those at 2.5 hours: c, $P < 0.05$; d, $P < 0.01$. C, control (baseline); PVR, pulmonary vascular resistance; RDV, right ventricular diastolic volume; SV, stroke volume.

Figure 2. Respiratory data in 12 dogs during mechanical ventilation without PEEP. Hgb, hemoglobin. The legend for the P values is given in Figure 1.

prŏduction of acute permeability pulmonary edema with oleic acid, the lung water content increased ($P < 0.01$) from the control (C) level of 6.3 to 14.6 ml/kg after 1 hr and subsequently increased ($P < 0.01$) further to 18.1 and 21.6 ml/kg after 2.5 and 4 hr respectively (Fig. 1). Simultaneously the pulmonary

vascular resistance increased more than 300% from a control measurement of 212 to 930 dynes·sec·cm^{-5} at 4 hr. The acute increase in the lung water content and pulmonary vascular resistance was associated with a 37% decrease in the right ventricular diastolic volume and a 57% decrease in the right ventricular stroke
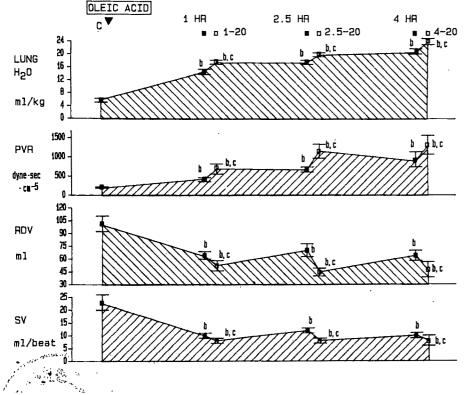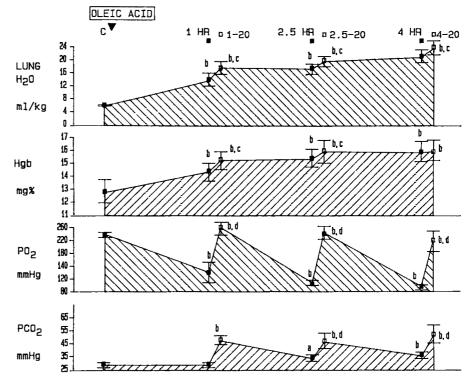

Figure 3. Hemodynamic data in 12 dogs before and after the addition of PEEP. Values are mean ± SEM. Each measurement is compared with the control (C) measurement: a, $P < 0.05$; b, $P < 0.01$. Measurements on PEEP at 2.5 and 4 hr are compared with the immediately preceding measurements not on PEEP: c, $P < 0.05$; d, $P < 0.01$. C, control; PVR, pulmonary vascular resistance; RDV, right ventricular diastolic volume; SV, stroke volume; 1-20, 2.5-20, and 4-20 refer to the addition of 20 cm H20 PEEP at each time interval.

Figure 4. Respiratory data in 12 dogs before and after the addition of PEEP. The legend for the P values is given in Figure 3. Hbg, hemoglobin.

volume. The most notable reductions in the right ventricular diastolic volume and stroke volume occurred 1 hr after the injection of oleic acid.

The fluid shift from the intravascular space to the interstitial and alveolar spaces of the lung with oleic acid pulmonary edema resulted in a progressive increase ($P < 0.01$) in the hemoglobin concentration in the blood from 12 to 16 g% and a decrease ($P < 0.01$) in Po_2 from 240 to 98 mm Hg (Fig. 2). Simultaneously the Pco_2 gradually increased from 30 to 37 mm Hg.

The application of 20 cm H_2O PEEP for a minimum period of 10 min at 1, 2.5, and 4 hr increased ($P < 0.05$) the lung water content at each measurement interval (Fig. 3). The lung water content increased from 14.6 to 18.2 ml/kg at 1 hr, from 18.1 to 21.2 ml/kg at 2.5 hr, and from 21.6 to 24.8 ml/kg at 4 hr. Each application of PEEP was associated with a 40% increase in the pulmonary vascular resistance and more than a 19% decrease in the right ventricular stroke volume ($P < 0.05$). The addition of PEEP also produced a decrease ($P < 0.05$) in the right ventricular diastolic volume ranging from 17% at 1 hr to 34% at 4 hr.

The increase in lung water content with the application of PEEP was associated with an increase ($P < 0.05$) in the hemoglobin concentration at 1 and 2.5 hr (Fig. 4). Notably, the application of PEEP increased ($P < 0.01$) the arterial oxygen tension to levels that closely approximated the control oxygen tensions. However, the increase in arterial oxygen tension was

also associated with an increase ($P < 0.01$) in arterial carbon dioxide tension.

Pleural pressure after the production of acute pulmonary edema did not differ significantly from the levels measured in the normal dogs. The pleural pressures consistently increased ($P < 0.01$) with each application of PEEP from mean values of 2 to 8.4 mm Hg. The mean arterial pressure decreased slightly from a control measurement of 129 to 118 mm Hg (not statistically significant) with the production of acute permeability pulmonary edema. With the addition of PEEP, the mean arterial pressure declined from a mean value of 118 to 96 mm Hg ($P < 0.05$). The transmural left ventricular end-diastolic pressure, the pulmonary artery wedge pressure, and the right atrial pressure decreased from the normal range with the production of acute permeability pulmonary edema and also with the addition of 20 cm H_2O PEEP. However, the changes in the transmural cardiac pressures were not statistically significant. The mean heart rate was 155 beats/min at the initiation of the investigation and the heart rate did not significantly change during the experiments.

Discussion

Effects of Oleic Acid

Oleic acid specifically damages the pulmonary capillary endothelium, causing perivascular, interstitial, and alveolar edema and atelectasis (16,19,20). In the

present investigation, oleic acid-induced acute permeability pulmonary edema was associated with significant increases in the lung water content and pulmonary vascular resistance, major reductions in right ventricular volume and stroke volume, and substantial decreases in the arterial oxygen tension.

Several hemodynamic mechanisms contributed to the reductions in the canine right ventricular volume and stroke volume after the development of acute permeability pulmonary edema. First, the abrupt and significant decrease in the right ventricular volume and the simultaneous increase in the lung water content within 1 hr after the right atrial injection of oleic acid are compatible with an acute reduction in the plasma volume. We believe that leakage of plasma fluid through damaged pulmonary capillaries into the interstitial and alveolar spaces of the lung acutely decreased the plasma volume and therefore the ventricular volume. Significant fluid accumulation was detected only in the lungs at autopsy. Furthermore, plasma volume changes of 8–14 ml/kg have been measured in subjects with acute hydrostatic pulmonary edema where the pulmonary capillary hydrostatic pressure exceeds the plasma colloid oncotic pressure. In such instances, fluid extravasates from the intravascular to the interstitial and alveolar spaces of the lung even though the pulmonary capillary membranes are intact (21,22). Plasma volume losses into the lung may be comparable or even greater with acute permeability pulmonary edema where the pulmonary capillary endothelium is disrupted (23). The progressive increase in the lung water content from 6.3 ml/kg to 24.6 ml/kg, the simultaneous increase in the hemoglobin concentration from 12 to 16 grams%, and the 37% decrease in the right ventricular diastolic volume are all consistent with an acute reduction in the plasma volume.

Second, the oleic acid damaged the pulmonary vascular bed and stimulated an increase in the pulmonary vascular resistance and thus an increase in pulmonary artery pressure. We believe that the substantial increase in pulmonary vascular resistance also caused a significant reduction in right ventricular function thereby decreasing the stroke volume. A reduction in right ventricular function is also indicated by the fact that the transmural cardiac pressures did not significantly decrease despite the marked reductions in the right ventricular volume. In the present investigation the increase in pulmonary vascular resistance decreased myocardial function, thereby limiting the reductions in intracardiac pressures. Consequently, the transmural cardiac pressure measurements did not precisely reflect the reductions in the ventricular volumes. These conclusions are supported by the work

of Halden et al. and also Pouleur et al. (20,24). Pouleur et al. demonstrated in normal dogs that when lung inflation increased pulmonary vascular resistance 32–87%, the pulmonary blood flow and the right ventricular power decreased more than 45% (24). The reductions in pulmonary blood flow and right ventricular power were not dependent on neural interaction, ventricular interference, or a decrease in coronary blood flow. Rather the decrease in ventricular power was explained by poor right ventricular adaptation to increased afterload (24).

Finally, the possibility that the thiopental anesthesia depressed myocardial contractility and decreased vascular resistance must be considered. Our dogs were not deeply anesthetized, however, as demonstrated by the fact that the mean arterial pressure was 129 mm Hg and the right ventricular volumes were within the normal range after the induction of anesthesia (10). The mean arterial pressures remained greater than 90 mm Hg throughout the study. Furthermore the transmural left ventricular end-diastolic pressures, pulmonary artery wedge pressures, right atrial pressures, and the right ventricular volumes did not significantly increase at any time during thiopental anesthesia. Hence it is unlikely that thiopental depressed myocardial contractility. However, thiopental did have a vagolytic effect. This barbiturate pharmacologic effect accounted for the tachycardia that was consistently present throughout the study after the induction of anesthesia (25).

Effects of PEEP in Oleic Acid Pulmonary Edema

The application of positive end-expiratory pressure to dogs maintained on mechanical ventilation increased the pleural pressure and significantly decreased the extrathoracic–intrathoracic venous gradient. Consequently the venous return to the right heart decreased. The increased pleural pressure caused by PEEP was passively transmitted to the heart and augmented the absolute cardiac filling pressures. However, the transmural cardiac pressures did not significantly change during the addition of PEEP because the right and left intracardiac pressures increased to a similar extent as the intrathoracic pressure. However the addition of 20 cm of H_2O PEEP significantly increased the lung water content and therefore further decreased the plasma volume. The increase in lung water content with PEEP was probably due to three mechanisms. Pulmonary hyperinflation may increase the lung microvascular hydrostatic pressure (26,27), which in turn may increase the extravasation of fluid through the damaged pulmonary capillaries into the interstitial and alveolar spaces of the lungs.

Positive end-expiratory pressure also increases the surface area of the extra-alveolar vessels, which may then contribute to edema formation (28,29). In addition, PEEP impairs the drainage of edema fluid by the pulmonary lymphatics (30). As a consequence of the decrease in venous return and the increases in the lung water content and pulmonary vascular resistance, the ventricular volumes and stroke volumes significantly declined with 20 cm H_2O PEEP (Fig. 3).

Our findings of a reduction in the right ventricular volume with PEEP contrasts with a report of cardiac changes in patients with adult respiratory distress syndrome (ARDS) who were treated with positive pressure ventilation and positive end-expiratory pressure (31). The report was based on ultrasonic measurements that suggested that PEEP may increase the right ventricular volume by shifting the interventricular septum into the left ventricular cavity. However, when these investigators directly measured right ventricular diastolic volume by thermodilution techniques, nearly half of their ARDS patients treated with PEEP had cardiac volume measurements that were normal or decreased (12). Positive pressure ventilation with PEEP may significantly change the geometric configuration and alter the position of the ventricles because of the displacement and physical compression of the heart by the inflated lungs (15,32). Such alterations may substantially decrease the diastolic compliance of the ventricles (15). Moreover, the hemodynamic effects of PEEP are determined, in large part, by the size of the intravascular volume. In hypovolemic and normovolemic subjects, PEEP generally decreases the cardiac output. However, positive end-expiratory pressure may normalize or increase the cardiac output in hypervolemic subjects (33,34). In subjects with vascular congestion, PEEP decreases the venous return to the heart and may improve cardiac pressure–volume relationships. In addition, PEEP may augment left ventricular function by increasing intrathoracic pressure and reducing ventricular wall stress (33,34). For these reasons the interpretation of cardiac ultrasonic measurements during one hemodynamic state does not apply to all conditions in which PEEP is utilized.

Respiratory Effects of PEEP in Oleic Acid Pulmonary Edema

In our dogs with oleic acid pulmonary edema, 20 cm H_2O PEEP decreased the intrapulmonary shunt, thereby increasing the arterial oxygen tension. Positive end-expiratory pressure converted small flooded alveoli to large unfolded air spaces containing similar amounts of fluid and also redistributed some edema

fluid to the interstitial and perivascular spaces of the lung (26,35). However, PEEP also increased the microvascular hydrostatic pressure of the lung and impaired the pulmonary lymphatic drainage of the edema fluid. Therefore the lung water content increased. Although the intrapulmonary shunt decreased with the use of PEEP, the arterial oxygen tension correlated poorly with the lung water content. This observation is supported by the work of other investigators (36,37).

Despite the improvement in the arterial oxygen tension with 20 cm H_2O PEEP, the concomitant increase in carbon dioxide tension indicates that gas exchange was not uniformly improved throughout the lung. Because the tidal volume and frequency of ventilation were held constant in the present investigation, the total lung ventilation did not change with PEEP. Furthermore, the fact that the pleural pressures increased to a similar level with each application of PEEP excludes the possibility of a decrease in alveolar ventilation because of a leak in the ventilator system. Rather, 20 cm H_2O PEEP increased the caliber of the airway, and therefore the anatomic dead space of the dog lungs, by significantly augmenting lung volume and increasing traction on the airway. In addition, PEEP substantially reduced the cardiac output and therefore the amount of blood perfusing the lung. Consequently, the portion of the lung with high ventilation but poor perfusion ratios significantly increased. In animals treated with high levels of PEEP, as much as 50% of the alveolar ventilation may be wasted in lung units having high ventilation–perfusion ratios (38,39). The increase in the carbon dioxide tension in the present experiments may be explained by an increase in the anatomic dead space and by an increase in regions of the lung with high ventilation but poor perfusion. In the present experiments we could not entirely exclude the possibility that the retention of carbon dioxide may have further contributed to the PEEP-induced decrease in the stroke volume by decreasing myocardial contractility.

In summary, in our investigation the decrease in right ventricular volume and stroke volume with oleic acid-induced pulmonary edema was primarily related to a reduction in the plasma volume and an increase in pulmonary vascular resistance caused by significant increases in the lung water content. Positive pressure ventilation with 20 cm H_2O PEEP increased the lung water content and the pulmonary vascular resistance and decreased the venous return to the heart.

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Comparison of Psychomotor Skills and Amnesia after Induction of Anesthesia with Midazolam or Thiopental

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In two groups of 31 healthy patients undergoing minor elective surgery, anesthesia was induced intravenously with either midazolam maleate, 0.2 mg/kg, or thiopental, 3.5 mg/kg. All subjects received 2 µg/kg fentanyl 5 min before the induction agents. Induction time with midazolam was significantly longer than with thiopental (97.1 ± 10.9 sec vs 59.4 ± 5.0 sec) and time to orientation postoperatively was significantly longer after midazolam (31.7 ± 4.2 min vs 11.0 ± 1.1 min). Continued recovery after orientation, measured by a series of psychomotor tests, was also significantly longer with midazolam than with thiopental. Anterograde amnesia was evident in 84.8% of the midazolam treated patients and in only 31.4% of the thiopental group. This degree of absence of recall was acknowledged positively by the affected patients. The protracted recovery period may limit the use of midazolam in short surgical procedures.

Key Words: ANESTHESIA, INTRAVENOUS—thiopental, midazolam. HYPNOTICS—benzodiazepines, midazolam, barbiturates, thiopental. MEMORY—amnesia. RECOVERY—psychomotor tests.

Midazolam, a water-soluble benzodiazepine with a more rapid onset of action and shorter plasma half-life than diazepam (1), has been proposed and used as an anesthetic induction agent for short surgical procedures (2). Midazolam has been compared to thiopental (3), methohexital (4), and diazepam (5) with respect to rapidity of onset and hemodynamic action. Although there are few data on midazolam's effect on psychomotor function, its amnestic qualities have been shown to be similar qualitatively to other benzodiazepines when given as a premedicant orally (6) or intramuscularly (7).

Recently, the number of patients involved in outpatient anesthesia and surgery has increased markedly (8). Recovery after these short procedures should be swift so that release from the postsurgery unit may be accomplished within a reasonable time. Because of the need for rapid return of normal psychomotor skills in the ambulatory setting, and because mida-

zolam has not been studied in regard to recovery of these functions, we investigated the time for recovery of psychomotor function with midazolam compared to the "standard" induction agent, thiopental, and assessed the short-term amnestic qualities of both drugs.

Methods

Sixty-two ASA I and II patients undergoing minor elective surgical procedures were included in this double-blind, parallel-group study. They were assigned randomly to receive either thiopental (31 patients) or midazolam (31 patients) for induction and maintenance of anesthesia.

On the morning of surgery, before any medication was given, all subjects were tested for various psychomotor skills:

1. Hand coordination (manual dexterity) was measured with the Purdue peg board. The patient was asked to remove and invert as many pegs on the board as possible in a 30 sec period of time. The number of pegs so rotated was recorded as the baseline score.
2. Vigilance was measured as follows: a piece of paper, 12 cm by 24 cm, was designed with groups of dots arranged in 25 rows with 12 groups of dots in each row. Each group of dots consisted of three, four, or five dots with several groups of four dots

arranged randomly in each row. The patient was asked to draw a line through each group containing four dots only, reading from left to right down the page. The number of lines completed in 3 min and the number of errors were recorded for the baseline score (9).

3. Spatial concepts were tested by instructing the patients to place six differently shaped blocks of wood in the appropriately shaped holes in a board. The time for completion of this test was recorded as the baseline control.

4. A series of digits was read to each patient, who was asked to repeat it. The series length began with four digits and was increased by one digit sequentially to a maximum of nine digits or until the subject could not correctly repeat the series. The longest series successfully completed was the baseline value for the individual patient (10).

These tests were performed before induction of anesthesia on the day of surgery and, after the operation when the patients were considered fully oriented in the recovery room, hourly for 6 hr. The rapidity of return towards baseline levels after anesthesia and surgery with midazolam or thiopental was compared. Statistical significance was determined by an arithmetic regression analysis.

In addition, each patient was shown a picture of a dollar bill before preoperative medication and was shown the same picture of a dollar bill again 6 hr postoperatively. Failure to remember having been shown the dollar bill preoperatively was considered an indication of retrograde amnesia.

Finally, the patients were shown ten pictures of common objects such as a house, chair, shoe, etc., at the time after the operation when they were considered fully oriented. They were asked to remember these pictures. Six hours postoperatively, a group of 20 pictures, including the original ten pictures, were shown to the patients. The patients were asked to identify those pictures that had been shown previously. Anterograde amnesia was considered total if none of the original pictures were recalled, partial if one to four pictures were remembered, and absent if five to ten pictures were recalled.

On the morning of surgery all subjects received 0.5 mg glycopyrrolate intramuscularly. In the preanesthesia holding area an 18-gauge intravenous Teflon catheter was inserted into the back of the nondominant hand and a saline–dextrose solution administered at a rate of 4 $ml \cdot kg^{-1} \cdot hr^{-1}$. In the operating room, 5 min before the induction of anesthesia, all subjects received fentanyl, 2 $\mu g/kg$ intravenously. After adequate preoxygenation, anesthesia was induced either with midazolam maleate, 0.2 mg/kg, or thiopental, 3.5 mg/kg, injected over 5 sec. Induction was considered complete when there was an absence of eye lid reflex and voluntary movement, and a lack of response to verbal command. The time from the injection of the induction agent until the successful induction of anesthesia was recorded.

Heart rate was measured constantly from the ECG, mean arterial blood pressure was obtained from an automated oscillometric device, respiratory minute volume was extrapolated from a 15-sec spirometry measurement, and end-expiratory CO_2 was transduced by an infrared capnograph. All variables were measured immediately before the anesthetic induction (control), within 1 min after the successful onset of anesthesia (after induction measurement), and periodically in our standard clinical fashion throughout the anesthetic course. Tracheal intubation was not performed and all patients breathed spontaneously. Anesthesia was maintained with 67% nitrous oxide and 33% oxygen, and increments of 25% of the initial induction dose of the tested agent were administered for a somatic response - that is, phonation, coughing, or movement. In the presence of an autonomic response, e.g., blood pressure or pulse rate increased 25% above control values or the onset of sweating or tearing, 25 μg incremental doses of fentanyl were given. Times for duration of surgery and anesthesia were taken from the standard anesthetic record. Anesthesia time was from the onset of anesthetic induction until the patient left the operating room.

In the recovery room, the subjects were graded according to the progress of their recovery from anesthesia: 1, asleep, no response to verbal commands, no lid reflex; 2, asleep, no response to verbal commands, lid reflex present; 3, drowsy, but responds to verbal commands—patient was considered awakening; 4, no drowsiness, converses normally, and personally feels awake. The subjects were judged oriented when there was no overt drowsiness and they were oriented to time, place, and self-identification. All psychomotor, amnestic, and emergence testing was performed by a trained observer without knowledge of the anesthetic agent. No patient was aware which drugs were used, and in the operating room all measurements were made by a physician not involved with the administration of anesthesia or the management of the case.

For anesthetic induction time, length of surgery and anesthesia, and time to orientation, statistical analysis between groups was by analysis of variance. Recovery of psychomotor skills was examined by the Cox proportional regression model and amnesia was compared by the Mantel–Haensgel test. Values are

Table 1. Demographic Comparison

	Midazolam	Thiopental
Number of patients	31	31
Age (yr)	36.1 ± 3.2	37.6 ± 2.8
Weight (kg)	62.2 ± 4.8	69.0 ± 5.1
Percent female	96.8	93.5
ASA I	22	24
ASA II	9	7

presented as the mean ± SEM unless otherwise noted; $P < 0.05$ was considered significant. The investigation was approved by the Human Research Committee at the University of California, Davis.

Results

There were no significant differences in the groups with respect to age, weight, sex distribution, or ASA classification (Table 1). There were no instances of failed induction of anesthesia. However, the time for induction of anesthesia was significantly longer with midazolam (Table 2). The maintenance dose of the induction agents was similar in both groups, but 50% more fentanyl was necessary to maintain analgesia in the patients receiving midazolam. The length of surgery was nearly equal in both groups, but the duration of anesthesia was slightly longer in the midazolam subjects. Likewise, patients receiving midazolam took longer to become oriented postoperatively than those receiving thiopental.

Cardiovascular and ventilation variables are shown in Table 3. The only significant difference between the two groups of patients appears in the relative postinduction hypoventilation of the thiopental group. The incidence of apnea (defined as more than 15 sec without a breath) was similar in both groups during induction of anesthesia, 59% and 68% for midazolam and thiopental, respectively.

Times for 75% of the patients to reach their preanesthetic baseline values in the various psychomotor tests are listed in Table 4. Patients given thiopental returned more rapidly to their control values in all tests. These differences were statistically significant for all skills except the spatial orientation examination.

In no patient was there evidence of retrograde amnesia. All patients successfully remembered having seen the dollar bill picture prior to any drug administration. On the other hand, there was a significantly greater lack of anterograde recognition of the common objects' cards among the midazolam patients (Table 5). More than 50% of the patients given thiopental had absence of anterograde amnesia whereas all the patients given midazolam had some degree of recall

Table 2. Comparison of Midazolam and Thiopental

	Midazolam	Thiopental
Time for induction of anesthesia (sec)	97.1 ± 10.9[a]	59.4 ± 5.0
Maintenance dose of induction agent (percent of induction dose)	66.7 ± 10.7	59.0 ± 5.0
Maintenance dose of fentanyl (µg/kg)	0.89 ± 0.08[a]	0.58 ± 0.04
Length of surgery (min)	17.6 ± 2.2	17.7 ± 2.4
Length of anesthesia (min)	28.1 ± 3.1[b]	22.6 ± 2.8
Time to orientation (min)	31.7 ± 4.2[a]	11.0 ± 1.1

[a]Differs from thiopental group; $P < 0.01$.
[b]Differs from thiopental group; $P < 0.05$.

deficit after they were judged awake and oriented in the recovery room—in fact, 84.8% of the midazolam patients recalled none of the previously shown pictures. This significant amount of anterograde amnesia lasted for at least 6 hr.

Discussion

Our study demonstrates that midazolam significantly prolongs recovery from anesthesia for short surgical procedures compared to thiopental. This delay has been observed by others, particularly in older patients (11). Crawford et al., using the Glasgow Coma Scale as an index of awareness, found significantly greater initial postoperative depression in patients receiving midazolam for anesthetic induction for minor surgery compared to those who received thiopental (2); yet by 60 min, both groups had recovered to near normal Coma Scale scores. Verma et al. also demonstrated that induction of anesthesia with midazolam was associated with a considerable increase (17 min) in recovery time of healthy patients undergoing therapeutic abortion in contrast to those receiving methohexital for induction of anesthesia (4). In both of these studies, patients' acceptance of midazolam was high and recovery times, while longer than those following the ultra-shortacting barbiturates, were reasonable for outpatient surgery. The time to orientation following midazolam in our investigation (31.7 ± 4.2 min) is near the range of acceptable for day-case surgery (12). However, the significant delay in return to baseline of the psychomotor tests was surprising and supports the observation that patients undergoing general anesthesia may be at risk if discharged without proper supervision (13).

The screening tests in our study, i.e., manual dexterity, vigilance, spatial concepts, and short-term memory, are considered moderately sensitive in detecting differences in the depressed performance of

Table 3. Cardiorespiratory Variables

	Midazolam	Thiopental
Mean arterial pressure (torr)		
Before induction	94.4 ± 2.5	91.2 ± 2.4
After induction	90.5 ± 3.0	85.4 ± 2.8
Pulse rate (beats/min)		
Before induction	75.8 ± 2.5	76.5 ± 2.8
After induction	77.2 ± 2.4	75.0 ± 3.0
Minute ventilation (L/min)		
Before induction	5.0 ± 0.5	4.5 ± 0.4
After induction	5.1 ± 0.8	3.0 ± 0.4[a]

[a]differs from midazolam group $P < 0.05$

Table 4. Psychomotor Skill Tests: Time for 75% of Patients to Reach Baseline Levels (min)

Test	Midazolam	Thiopental
Hand coordination (pegs turned in 30 sec)	320[a]	250
Vigilance (dots crossed correctly)	281[b]	194
Spatial Concepts (blocks inserted)	241	151
Short-term learning (digits repeated correctly)	114[b]	48

[a]Differs from thiopental group; $P < 0.05$.
[b]Differs from thiopental group; $P < 0.01$.

Table 5. Anterograde Amnesia: Percent of Patients Evaluated

Drug	Absent	Partial	Complete
Midazolam	0	15.2	84.8[a]
Thiopental	51.4	17.1	31.4

[a]Differs from thiopental group; $P < 0.01$.

subjects given various hypnotics, sedatives or placebo (14). In spite of the "middle-of-the-road" discriminatory value of our tests, the differences between midazolam and thiopental were obvious and significant. We used the point where 75% of the patients had returned to their respective control values for comparative purposes, in an attempt to reduce the effect of a singular aberrant response in any one test.

The time for induction of anesthesia in our investigation agrees closely with earlier studies (15,16), but more recent clinical investigations have demonstrated midazolam induction times less than one half of what we observed (2,4). However, in both the latter cases a significant premedication was used and in one study 50% more midazolam was given for the induction dose (4). At our dosages, the period during onset of anesthesia was remarkably smooth and progressive, without sudden changes in cardiovascular or respiratory variables.

A small decrease in blood pressure was noted in most patients following the induction of anesthesia. This amount of change is similar to the reports of other observers (17,18) and bears little clinical significance for the healthy patient. Interestingly, in our study midazolam caused less respiratory depression after induction than thiopental did. However, with more sophisticated measuring techniques (CO_2-ventilatory response slopes) in nonoperative subjects, other investigators have shown that midazolam is associated with more respiratory depression than equivalent doses of thiopental (19), particularly in the form of a prolonged recovery of the response slope (20). Our postinduction measurements were made approximately 1 min after the successful induction of anesthesia, the point at which Gross and colleagues found the greatest respiratory depression from midazolam (20). Yet in another clinical study of patients premedicated with narcotics, there was less respiratory depression (measured by the incidence and length of apnea) with midazolam than with thiopental (21).

Possibly in the operating room setting of the clinical studies, with the stimulus of noise, skin preparation and draping, patients given midazolam are more sedated, but less anesthetized, than patients given thiopental, so that some respiratory depression is attenuated in the midazolam patient.

Although our patients had no retrograde amnesia, there was a marked difference between the midazolam and thiopental subjects in the magnitude and incidence of anterograde recall. With midazolam, lack of picture recognition lasted 6 hr (the limit of our observation), which is somewhat longer than the reported effect in unanesthetized patients (22). Other demonstrations of anterograde amnesia with midazolam support our findings of this significant antirecognition effect in midazolam-treated patients (23). The lack of memory of the preoperative and postoperative experience after administration of the drug was viewed as pleasant in all patients interviewed and may be considered a positive attribute in the anesthetic regimen.

In conclusion, we have demonstrated that midazolam maleate is an effective inducing agent for anesthesia in healthy patients, but that it delays recovery of psychomotor function compared to thiopental. This prolongation of return to normal function may alter its acceptance as a primary agent for short cases and ambulatory surgery. Midazolam's amnestic qualities were accepted positively by the patients involved, but surgeons and anesthesiologists should be aware of it when discussing the results of surgery postopera-

tively with the patient or giving verbal instructions for home care after apparent recovery from the anesthetic.

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Epidural Analgesic Techniques in the Management of Cervical Pain

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ROWLINGSON JC, KIRSCHENBAUM LP. Epidural analgesic techniques in the management of cervical pain. Anesth Analg 1986;65:938–42.

The injection of depot steroids into the cervical epidural space can maximize the conservative management of patients with cervical radiculopathy. We retrospectively studied 25 patients wtih cervical radiculopathy who received a total of 45 epidural injections of steroids. Sixty-four percent of the patients had a good or excellent response to cervical epidural steroid injection, whereas other conservative treatment modalities had not helped them. The patient's history and a description of the pain and the corresponding neurological abnormalities present were of value in the selection of patients who were most likely to respond favorably to epidural steroids, whereas laboratory studies were not as useful. Anesthesiologists, many already familiar with the use of epidural steroid injection in the treatment of low back pain, should add to their armamentarium the use of such techniques in the management of patients with acute and chronic cervical radiculopathy.

Key Words: PAIN, CERVICAL—treatment. ANESTHETIC TECHNIQUES, EPIDURAL—cervical

The field of anesthesiology has expanded in recent years to encompass more than the management of patients in the operating room and intensive care settings. For instance, anesthesiologists have become progressively more involved in the management of patients with chronic pain (1). Nerve block techniques, which are part of the anesthesiologist's armamentarium, are often requested in the evaluation and/or treatment of acute and chronic pain conditions. A good example of this is the well-established use of lumbar epidural steroid injections in the management of sciatica and radicular low back pain (2–6).

Cervical epidural steroid injection (CESI), although not as familiar to many anesthesiologists, can be useful in the management of selected patients experiencing problems with acute and chronic neck, shoulder, and arm pain (7–9). The purpose of this retrospective study is to define the clinical indications for cervical epidural steroid injection and to document its effectiveness or lack thereof. All patients had been referred for epidural steroid injections by orthopedic surgeons and neurosurgeons familiar with our positive results with such treatment of their patients with low back pain. All patients studied had persistent complaints of pain and restricted activity even after receiving conservative therapy for weeks or months before referral to us for evaluation and treatment. No control group was available for comparison.

Methods

A retrospective study was undertaken of the 45 cervical epidural steroid injections performed over the past 3 yr at the University of Virginia Department of Anesthesiology Pain Management Center on 25 patients with cervical radiculopathy. The mean age of the patients was 46 yr, with a range from 26–75 yr. Sixteen patients were male; nine were female. The average duration of symptoms was 15.1 months. The referral diagnosis of cervical radiculopathy was substantiated by a history of radicular pain from the neck into the arm, neurological changes found upon physical examination, and/or laboratory study results reviewed during the evaluation of the patient in the Pain Management Center (Table 1). No patient had a history of prior cervical spine surgery, malignancy (to explain the pain), or allergic/idiosyncratic reaction to previous injections with local anesthetics, nor were any taking major anticoagulant medications.

Verbal consent was obtained before each patient received CESI and after the likely etiology of the pain was explained and the rationale for the use of CESI was discussed. Each patient was placed in a sitting position with both feet resting on a stool and the neck flexed so that the forehead rested comfortably on a pillow placed in front on the edge of a stretcher. The prominent C-7 vertebral spinous process, easily pal-

Table 1. Patient Data

| Patient | History | Physical Exam | | | Lab Studies | | | | Duration (months) | Number of blocks | Response | Follow-up (months) |
		Sensory	Motor	Reflex	x-Ray	EMG	CT	Myelogram				
1	P	P	P	N	P	N	—	—	3	1	E	1
2	P	P	P	N	—	N	—	P	4	1	E	1
3	P	P	N	N	—	P	—	—	5	1	E	3
4	P	P	N	N	P	N	—	—	12	3	E	10
5	P	P	P	P	—	N	P	—	4	2	E	1
6	P	P	N	N	—	P	—	P	6	1	E	1
7	P	P	P	N	—	N	N	N	42	3	G	2
8	P	P	P	N	N	P	—	P	36	2	G	11
9	P	P	P	P	—	P	—	—	24	1	G	1
10	P	N	P	N	N	N	—	—	4	1	G	4
11	P	N	N	N	—	P	—	P	2	1	G	22
12	P	P	P	N	—	—	N	—	48	3	G	2
13	P	P	P	P	—	P	—	P	4	2	G	13
14	P	P	N	N	—	P	—	—	4	1	G	1
15	P	P	P	N	—	P	—	—	4	2	G	1
16	P	N	N	N	P	—	P	P	60	2	G	3
17	P	P	N	N	—	N	—	—	12	1	F	1
18	P/N	N	N	N	P	P	—	—	7	4	F	1
19	P/N	P/N	P/N	N	N	N	—	—	5	1	F	9
20	P	P	P	P	N	P	—	—	1	2	F	27
21	P	P	P	P	—	P	—	—	11	2	F	4
22	P	P	N	N	—	N	P	—	48	2	F	2
23	P	P	N	N	—	P	—	—	8	1	O	3
24	P	N	N	N	P	P	—	N	9	2	O	60
25	P	P	P	N	—	—	—	P	6	3	O	2

Abbreviations: EMG, electromyograph; CT, computed tomography; P, positive; N, negative; P/N, neutral; E, excellent; G, good; F, fair; O, poor.

pated when the patient's neck is flexed, was identified, and the C6–7 or C7–T1 interspace was located by its superior or inferior relationship to the C-7 process. The skin of the neck region was cleansed and draped in an aseptic fashion.

A skin wheal of 1% lidocaine without epinephrine was placed in the midline at the interspace chosen for the injection. A 17-gauge, Weiss (winged) epidural needle (Travenol) was introduced in the midline, angled 30° caudad off the perpendicular plane with the skin, and advanced into the interspinous ligament (10). When the needle was stabilized in the ligament, the stylet was removed and the epidural needle filled with local anesthetic or saline until an obvious dome of fluid was visible at the hub. The needle was then advanced slowly towards the epidural space using the wings of the needle for accurate control. If bone was encountered, the needle was appropriately redirected to a line of approach through the ligaments. Entry into the epidural space was evidenced in all cases by the obvious disappearance of the hanging drop through the needle.

After negative aspiration through the needle, a total of 2 ml of 2.5% (50 mg) triamcinolone diacetate (Aristocort Intralesional—Lederle) mixed with 2 ml of 1% lidocaine without epinephrine was injected. (This dose of steroid is the same as that used in lumbar epidural steroid injections and is well-tolerated by the patients.) The needle was removed and the patient was placed on a stretcher with the side of the pain complaints dependent. The correct placement of the injection was usually confirmed by an appropriate dermatomal decrease in sensation and/or relief of pain in the affected extremity or shoulder region. There were no complications with this technique, and no patient suffered an aggravation of symptoms caused by the therapy. Intravenous infusions were not routinely used, but suction and oxygen administration equipment were always readily available, as were drugs and equipment for full resuscitation.

The lateral decubitus position was used after the placement of steroids into the cervical epidural space to allow the steroid (which settles to the down side in the mixture with local anesthetic or saline) to bathe the affected nerve root(s). After 10 min the patient was allowed to rest in the supine position until completely recovered from the nerve block. Thereafter, the patient was permitted progressively to regain the erect posture as tolerated before being discharged from our outpatient facility. The patients continued to use the nonsteroidal antiinflammatory drugs they had been using before the performance of the cervical epidural

steroid injection, and no restrictions were placed upon their activities. If repeat epidural blocks were deemed necessary, they were performed at 2-week intervals to a total of three blocks (although one patient in our study group did receive a fourth block some 6 months after the first series of three blocks).

Results

Twenty three of 25 patients (92%) presented with a positive history for cervical radiculopathy characterized by neck pain that radiated into the upper extremity. Two of 25 patients (8%) presented with neck pain that radiated only to the shoulder. Physical examination revealed a sensory deficit to pinprick in 20 of the 25 patients (80%). All sensory deficits correlated with an appropriate dermatomal distribution except in one patient in whom the sensation in the entire limb was diminished. Motor weakness was present in 14 of 25 (56%) patients. All deficits conformed to an anatomic myotomal pattern except in one patient in whom generalized weakness was noted. (This is the same patient mentioned above who had a sensory change involving the entire upper extremity.) Diminished reflexes were noted in only five of the 25 (20%) patients, but each of the five patients had a positive history for radicular pain and sensorimotor changes.

Laboratory studies included x-rays and computerized tomography (CT) of the cervical spine, as well as electromyography (EMG) and myelography. Not every patient had each of these tests (Table 1). Nine patients had x-rays of the cervical spine. Five of the nine x-rays showed relevant degenerative bony changes. Twenty-two patients had EMG studies of the upper extremity. Thirteen of these tests showed changes consistent with radiculopathy. Only five patients had CT studies, of which three were positive for cervical spinal cord compression and/or nerve root abnormalities. Nine patients had myelograms, with seven of the nine studies showing spinal cord and/or nerve root compression.

Clinical responses to CESI fall into four categories: excellent, good, fair, and poor. The average follow-up was 8.9 months after therapy. An excellent response was defined as complete resolution of the presenting symptoms. A good response was judged to be greater than 75% improvement in symptoms with full resumption of the patient's lifestyle. A fair response was defined as mild improvement in the patient's condition, whereas a poor response indicated little or no improvement.

The excellent responses were achieved in 24% (6/25) of the patients. An average of 1.5 blocks per patient was performed. All patients in this group had positive histories of radicular pain and anatomic sensory deficits. Sixty-seven percent of the patients with excellent responses (4/6) had motor weakness and none had abnormal reflexes. Radiographic studies of two patients in this group showed significant bony abnormalities. All six patients underwent EMG, but only two of these tests demonstrated radiculopathy. The one CT scan performed showed posterior and right lateral disc herniation at C4-5 and C5-6. Of the two myelograms performed on patients in this group, both showed abnormalities. The average duration of symptoms in this group was 5.6 months and the average follow-up period was 2.8 months.

Ten patients (40%) obtained a good response from the cervical epidural blocks. The patients in this group received an average of 1.8 blocks. All patients in this group had positive histories of radicular pain, and seven patients (70%) had both an anatomic sensory deficit and decreased motor strength. Twenty percent had decreased deep tendon reflexes. Two patients in the good response group had radiographic studies, one of which showed abnormalities. Of the eight EMG studies performed, six were consistent with radiculopathy. One of the two CT scans performed reported abnormal results. Five patients underwent myelography and four of these studies demonstrated significant compression of the spinal cord and/or nerve roots. Patients in this group had their symptoms for an average of 22.2 months and were observed for an average of 6 months after treatment.

A fair response was obtained in six patients (24%). An average of two blocks was performed on patients in this group. Four patients (66%) had a history consistent with radicular symptoms extending into the upper extremity. The other two patients in this group described neck and shoulder pain without any extension into the upper extremity. Four patients had sensory deficits (66%) and two had motor weakness. One patient had sensory and motor abnormalities that proved to be nonanatomic in distribution. Of the six patients in this group, two had decreased deep tendon reflexes. Three radiographic studies were performed, but only one showed abnormal results. All patients underwent an EMG, the results of which were consistent with radiculopathy in each case. The one CT scan performed was reported as abnormal. No myelograms were performed on patients in this group. The average duration of their symptoms was 14 months and of their follow-up 7.3 months.

Three patients had poor responses. Each patient received an average of two cervical epidural blocks. All had positive histories of radicular pain, two (67%) had sensory changes, and only one patient had decreased motor strength. No reflex abnormalities were

noted in this group. One patient had cervical spine x-rays obtained, and two patients had EMG studies. All of these studies showed abnormal results. The one CT scan performed did not show any abnormality. Of the two myelograms performed, one reported abnormal results. These patients had an average duration of symptoms of 7.6 months and required the longest follow-up, averaging 10.8 months.

Discussion

The use of steroid injections in the cervical epidural space in the management of pain in the neck, shoulders, and upper extremities has been suggested by other authors as a logical extension of a popular technique commonly applied in the lumbar region for the management of low back pain (8,9). However, these reports do not restrict CESI only to patients with radiculopathy, which is the condition for which lumbar epidural blocks with steroids are classically done. Catchlove and Braha recommend the use of cervical epidural procedures as part of an overall therapeutic program for cervical pain, but they did not use steroids in their injectate and they primarily report results in patients with muscle contraction-tension headaches and associated neck pain (7).

In our retrospective study, all patients had cervical radiculopathy. Of the 25 patients reviewed, 16 (64%) obtained a good or excellent response from CESI with full resumption of their daily activities and *at least* a 75% improvement in their pain complaints. Although it is difficult to study the exact effectiveness of CESI for cervical radiculopathy retrospectively, these patients had not previously experienced this degree of relief with traditional conservative measures, such as analgesics, nonsteroidal antiinflammatory drugs, cervical traction, and activity restriction. The improvement associated with CESI lasted for at least 6 months, after which time most of the patients were lost to further follow-up. Presumably if their symptoms had recurred, they would have reestablished contact with their primary physician at the University Medical Center.

All patients in the good and excellent response groups had positive histories of radicular pain. However, this feature alone does not discriminate those patients who are most likely to respond favorably to cervical epidural steroid placement. This conclusion is supported by the fact that in our study all three of the patients with poor results also had positive histories of radicular pain. However, when this aspect of the patient's history is coupled with the presence of physiologic sensory and motor deficits, the likelihood of a positive response to CESI increases. If the

two patients with vague complaints of pain and/or nondermatomal sensory deficits and nonmyotomal motor weakness are considered to have negative findings for cervical radiculopathy, the remaining 23 patients all had findings that were positive for radiculopathy in at least two of the three diagnostic categories (history, physical examination, and laboratory studies). Of these 23 patients, 16 (70%) had good or excellent results following CESI. Thus, positive findings in two of the three sources of information (history, physical examination and laboratory studies) seem to define satisfactory criteria for the consideration of performing CESI in patients with radicular cervical pain.

The diagnosis of cervical radiculopathy may be based only upon clinical findings. Our study suggests that the most appropriate patients for CESI would be those in whom both the history and physical examination are positive for cervical radiculopathy. Additional confirmation of the diagnosis may be sought through the use of laboratory tests when the history is less than specific or the patient's physical examination is near normal. That EMG results were almost noncontributory to the diagnosis in the good/excellent response group was surprising, especially because the tests were performed well after the time (3–4 weeks) when positive changes demonstrating radiculopathy should have been found (11).

It is worthwhile to mention that depot steroid preparations are topically applied to the neuraxis based upon the presumption that the patient's symptoms are due to inflammatory changes in nerve roots in the epidural space (5). Therefore, if inflammation is not contributing to the patient's symptoms, as might occur with longstanding complaints that reflect scarring in the nerve roots, no persistent favorable response to epidural steroid placement would be expected. Admittedly, we lack specific diagnostic tests to assess the inflammatory component of radicular symptoms, and this fact reinforces making the diagnosis based upon the clinical presentation. One may actually offer the first CESI as a diagnostic procedure. It may take 24–72 hr after the effect of the local anesthetic has worn off for the favorable effect of the steroid to become clinically evident. Thus, in a patient who does not improve after CESI, nerve root fibrosis rather than inflammation (which should respond to the potent antiinflammatory action of depot steroid drugs) may be the more significant etiology of the patient's complaints of pain.

Our patients demonstrated a very favorable degree of acceptance of this particular regional anesthetic technique. Even Catchlove and Braha's patients, who had cervical epidural catheters placed, tolerated the procedure well and with a minimum of complications

(7). We believe that acceptance is in large part due to our explaining both the rationale for and the technique of CESI. The description of the procedure includes a caution that the patient's radicular symptoms may be transiently exacerbated because of the positive pressure nature of the injection and the temporary change in the pressure dynamics in the cervical epidural space. The dose of triamcinolone diacetate is similar to that used in the management of lumbar radiculopathy. The needle should be cleared of steroid before it is withdrawn to prevent the development of a nonhealing track along the needle path (12).

To enhance the ultimate therapeutic response in patients with cervical radiculopathy, other treatment should also be recommended in the ongoing therapeutic program (7,8). Cervical epidural steroid injection is just one of the treatment options. Our patients were encouraged to continue to take nonsteroidal, antiinflammatory drugs and to participate in rehabilitative physical therapy on a regular daily basis. When the patient's pain can be effectively reduced, the need for potent analgesic medications is eliminated and the consideration of invasive surgical procedures (with their attendant prolonged recovery) will be diminished. Also, the patient's attitude about recovery will be biased in such a way that he will more readily participate in rehabilitative physical and social programs. Pawl et al. showed that at least 50% of patients with pain related to cervical discogenic disease could expect pain relief without resorting to surgery when a program of nonoperative treatments is used (8).

The results of this study indicate that CESI can be safely performed in patients with cervical radiculopathy. The diagnosis is most likely to be made based upon positive aspects of the patient's history and physical examination. Sixty-four percent of patients had a good or excellent response. This result compares favorably with the work of Pawl et al. who observed better than 50% improvement in patients with cervical discogenic disease. The authors suggest that CESI may be an effective intervention for anesthesiologists in the management of patients with cervical radicular pain. Ultimately, well-controlled, prospective studies are necessary to validate the actual effectiveness of CESI in cervical radiculopathy.

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Hepatic and Renal Clearances of Lidocaine in Conscious and Anesthetized Sheep

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Sheep were implanted with cannulae to study blood flow through, and drug extraction by, the lungs, kidneys, liver, and gut. Lidocaine, infused to a steady state in conscious sheep, caused no significant changes in cardiac output or regional blood flow, and was cleared principally by the liver, where the extraction ratio usually exceeded 0.9, and by the kidneys, where the extraction ratio was 0.1–0.2. There was no detectable clearance by lungs or gut. Under general anesthesia with 1.5% halothane, the cardiac output and renal and hepatic blood flows were decreased to means of 77, 44, and 79% of mean control values, respectively, but hepatic

and renal extraction ratios of lidocaine were not systematically altered, so that regional clearances of lidocaine were not significantly different from those in conscious animals. There was evidence that the total body clearance of lidocaine exceeded the sum of the directly measured regional clearances in both control and general anesthesia studies. These equivocal findings of the effects of general anesthesia on lidocaine clearance are at variance with unequivocal findings of reduced regional clearances of other drugs tested in this preparation.

Key Words: PHARMACOKINETICS—lidocaine. ANESTHETICS, LOCAL—lidocaine. LIVER—lidocaine clearance. ANESTHETICS, VOLATILE—halothane.

The clearance of lidocaine may be increased or decreased by factors which, respectively, increase (e.g., ingestion of food) (1) or decrease hepatic blood flow (e.g., β-adrenoceptor blockade) (2). It may be postulated that clearance of lidocaine will be affected by the disturbances of hepatic blood flow known to occur in the perioperative period (3), and preliminary results support this postulate (4).

It is becoming apparent that general anesthesia with halogenated hydrocarbons such as halothane does, in fact, decrease the clearance of many drugs. These effects of general anesthetic agents are mediated not only through their hemodynamic effects, but also through depressant effects on intrinsic clearances of drugs at the liver, kidney, and lungs (5). Because different anesthetic agents affect the circulation to different extents, it is not possible to explain changes in

clearance of drugs in terms of changes in blood flow and/or extraction ratio unless specific knowledge of each combination of drug and anesthetic agent is available. Not surprisingly, Burney and DiFazio (6) found it difficult to interpret changes in the elimination of lidocaine in dogs receiving nitrous oxide or halothane anesthesia without knowledge of the effects on each of the variables of the clearance equation.

Recently, we have described an in vivo animal preparation in which the effects of anesthetics on hemodynamics and drug elimination may be studied individually (7–9). We have used this preparation to study the clearance of lidocaine and, in particular, to study the effects on lidocaine clearance of the altered hemodynamics caused by halothane anesthesia.

Method

Animal Preparation

The studies were carried out to standardized protocols in sheep with chronic intravascular catheters. Both the surgical preparation of the animals and the methods for measuring regional blood flows and drug

clearances have been described in detail elsewhere (7–9). However, a brief description of those aspects pertaining to the disposition of lidocaine is presented here.

Sheep were acclimatized to metabolic crates and then, under general anesthesia, intravascular catheters were placed into the left renal vein, right hepatic vein, right atrium, the pulmonary artery via the right jugular vein, and the aortic root via the right carotid artery. Additional catheters were placed in the mesenteric and portal veins via an abdominal incision. On recovery, the catheters were attached to a high pressure–low flow continuous flushing system, and 2 weeks were allowed for the animal to recover from surgery. Subsequently, by simultaneously sampling from these catheters, blood flow through and drug extraction by kidney, lung, liver, and gut could be measured repeatedly without need for the animals to be restrained. Cardiac output was measured by thermodilution, liver blood flow was measured by continuous indicator dilution using ^{125}I-iodohippurate (IOH) infused into the mesenteric vein, and kidney blood flow was measured by means of the Fick principle and IOH.

Control-Drug Studies

A series of four control-drug studies were performed. In each control-drug study, seven sets of control measurements of cardiac output, and renal and hepatic blood flows were made 10 min apart over 1 hr. Lidocaine was infused using a two-stage infusion to hasten the production of steady state blood concentrations. A loading dose of 11.8 mg/min for 15 min was followed by a maintenance infusion of 4.7 mg/min for 75 min. The last hour of the maintenance infusion was regarded as a period of "steady state." Seven sets of hemodynamic measurements and blood samples from all appropriate sites were obtained 10 min apart over this period for determination of the effects of lidocaine infusion on hemodynamics and for determination of the regional clearances of lidocaine. Additional arterial blood samples were obtained 5 min apart for lidocaine concentration determinations both during the loading infusions and after the cessation of the maintenance infusion to facilitate the calculation of the mean total body clearance.

General Anesthesia Studies

Studies were performed in each of the same animals. In these studies, the control period was shortened to four sets of measurements made 10 min apart over 30 min. Anesthesia was induced with sodium thio-

pental (20 mg/kg intravenously), a cuffed endotracheal tube was introduced, and anesthesia was maintained with 1.5% halothane and positive pressure ventilation using 40% oxygen (balance nitrogen). The animal was placed in its normal lying position with the sternum supported on a foam rubber bolster and the legs tucked comfortably beneath it. After 60 min, the lidocaine infusion regimen, hemodynamic measurements, and the blood sampling schedule of the control-drug study were repeated. During anesthesia, intravenous saline was infused as required and the mean arterial pressure was maintained to within a mean of 90% of the preanesthesia values.

Kinetic Analysis

During the steady state period, regional lidocaine clearances were determined from the products of blood flows through (Q), and directly measured extraction ratios (E) across, the relevant organs. The effects of anesthesia were assessed by their effects on hepatic intrinsic clearances, which were calculated from Q and E according to the constant blood binding models and the following equations (10,11): for intrinsic clearance (Cli) of the "well stirred" model, Cli = $(Q \cdot E)/(1 - E)$; for intrinsic clearance of the "parallel tube" model, Cli = $-Q \cdot \ln(1 - E)$. The mean total body clearance of lidocaine was determined from the ratio of the maintenance dose rate to mean arterial blood concentration during the steady state periods.

Drug Concentration Analysis

The drugs were infused as the hydrochloride salts, but amounts and concentrations are expressed as the base. Lidocaine concentrations in whole blood (1 ml) were determined by a previously published method based on solvent extraction and gas–liquid chromatography with nitrogen selective detection (12). Mepivacaine (10 μg) was used as an internal standard. The column was packed with 3% OV17 on Gas Chrom Q and operated at 250°C with nitrogen carrier gas (30 ml/min). Retention times for lidocaine and the internal standard were 1.2 and 2.2 min, respectively.

Data Analysis

The hemodynamic and kinetic parameters during the drug steady state periods were each expressed as a percentage of the mean value of the corresponding parameter in the control period preceding anesthesia on that day and compared using Student's t-test. The effects of anesthesia on the regional clearances of lidocaine were assessed by comparison to values ob-

Table 1. Hemodynamic and Drug Disposition Data in Control-Drug Studies

Study	CO (L/min)	Ca (mg/L)	CL (L/min)	ERh	HBF (L/min)	CLh (L/min)	ERr	RBF (L/min)	CLr (L/min)	CLiWS (L/min)	CLiPT (L/min)
Before lidocaine infusion											
1	3.1 ± 0.2	—	—	—	1.42 ± 0.24	—	—	0.88 ± 0.11	—	—	—
2	4.2 ± 0.5	—	—	—	1.36 ± 0.28	—	—	0.63 ± 0.08	—	—	—
3	3.7 ± 0.4	—	—	—	1.63 ± 0.35	—	—	0.76 ± 0.04	—	—	—
4	4.0 ± 0.3	—	—	—	1.39 ± 0.36	—	—	0.69 ± 0.06	—	—	—
During lidocaine infusion											
1	3.0 ± 0.5	3.6 ± 0.5	1.29	0.96 ± 0.02	1.50 ± 0.31	1.43 ± 0.31	0.13 ± 0.15	0.89 ± 0.06	0.11 ± 0.13	36	4.8
2	4.6 ± 0.4	2.5 ± 0.7	1.91	0.91 ± 0.02	1.07 ± 0.17	0.97 ± 0.15	0.11 ± 0.29	0.80 ± 0.05	0.12 ± 0.28	11	2.6
3	3.7 ± 0.2	5.6 ± 0.8	0.84	0.95 ± 0.01	1.39 ± 0.23	1.43 ± 0.15	0.11 ± 0.07	0.87 ± 0.04	0.10 ± 0.06	29	4.2
4	4.4 ± 0.2	1.5 ± 0.2	3.23	0.65 ± 0.03	1.64 ± 0.25	1.22 ± 0.39	0.16 ± 0.11	0.61 ± 0.03	0.12 ± 0.12	3.5	1.3

Abbreviations: CO, cardiac output; Ca, lidocaine arterial blood concentration; CL, lidocaine mean total body clearance; ERh, lidocaine hepatic extraction ratio; HBF, hepatic blood flow; CLh, lidocaine hepatic clearance; ERr, lidocaine renal extraction ratio; RBF, renal blood flow; CLr, lidocaine renal clearance; CLiWS, mean intrinsic hepatic clearance of lidocaine, "well-stirred" model; CLiPT, mean intrinsic hepatic clearance of lidocaine, "parallel tube" model.
[a] Values are mean ± SD.

tained in control-drug studies. As the effects of anesthesia on hemodynamics have been the subject of a previous report (13), only those aspects that directly concern the interpretation of the disposition of lidocaine will be reported here.

Control-Drug Studies

Lidocaine did not markedly influence hemodynamics at mean arterial blood concentrations between 2.5 and 5.6 mg/L (Table 1), but the renal extraction ratio of iodohippurate was reduced to 90 ± 6% of the prelidocaine values ($P = 0.06$, one-tail test).

Lidocaine was not extracted detectably across the pulmonary circulation during the steady state period. Although studies were not performed in each of the animals, there was no significant net extraction of drug across the gut; mean portal venous concentrations of lidocaine were within 10% of the mean simultaneous arterial concentrations in 30 pairs of measurements. Thus, hepatosplanchnic elimination may be reasonably described as hepatic.

Lidocaine underwent substantial hepatic extraction, the majority of values being greater than 0.9. At the same time, hepatic blood flow ranged from 1.1 to 1.6 L/min in the different studies. Thus, hepatic clearance ranged from 1.0 to 1.4 L/min (Table 1). Hepatic intrinsic clearance calculated from these data reflected the variability in the hepatic extraction ratio and varied tenfold and fourfold for the "well-stirred" and "parallel tube" model calculations, respectively. The hepatic extraction ratio of lidocaine was not correlated with either cardiac output or hepatic blood flow.

The renal clearance of lidocaine fluctuated inexplicably during the course of most studies despite a consistent renal blood flow. Despite this, mean renal clearances varied little between studies but were small compared to hepatic clearances. In two of the studies the mean total body clearance of lidocaine was considerably greater than the sum of the mean clearances by lung, kidney, liver, and gut, suggesting that organs or regions other than these contributed to lidocaine clearance.

General Anesthesia Studies

In the presence of general anesthesia, mean arterial concentrations of lidocaine were an average of 150% of those in the control-drug studies (Table 2). This increase, overall, was not statistically significant despite a doubling of lidocaine concentrations in two studies.

Hemodynamic changes occurring under general anesthesia included decreased cardiac output, hepatic

and renal blood flows, and these were of similar magnitude to those reported to occur in this preparation under general anesthesia and infusion of a variety of other drugs (13). Specifically, under general anesthesia during the last hour of the lidocaine infusion, the cardiac output, renal blood flow, hepatic blood flow, mean arterial pressure, and heart rate all decreased to mean ± SD values of 77 ± 25, 44 ± 9, 77 ± 38, 89 ± 8, and 103 ± 15% of their corresponding values before anesthesia.

Under general anesthesia, the mean hepatic extraction ratio and clearance of lidocaine were mean ± SD values of 109 ± 17 and 79 ± 38%, whereas mean intrinsic clearance calculated according to "well-stirred" and "parallel tube" model equations were, respectively, 129 and 104% of their values in corresponding control-drug studies. These changes were not statistically significant. In the two studies in which the mean arterial concentrations doubled (2 and 4), the mean hepatic blood flow and clearance was reduced to one half in one study and remained essentially unaltered in the other. Conversely, in the other two studies (1 and 3) the mean arterial concentrations of lidocaine remained essentially unaltered, but the mean hepatic blood flow and clearance halved in one study and remained unaltered in the other. In studies 1, 2, and 4 the mean total body clearance was markedly less under general anesthesia than in the control-drug studies and disproportionate to the change in hepatic clearance, suggesting that additional mechanisms of clearance were decreased also.

Discussion

Despite the production of lidocaine arterial blood concentrations in the antidysrhythmic "therapeutic range" there were no appreciable hemodynamic effects in conscious animals. Increased cardiac output or hepatic blood flow, with the potential for increasing the clearance of lidocaine during the course of the infusion, could have been expected from studies in humans (11,14). On the other hand, from studies in the isolated perfused rat liver systematic decreases in hepatic extraction ratio could have been expected during the steady state period (15). Others have reported decreased mean total body clearance (by 50%) and hepatic extraction ratio (by 66%) of lidocaine upon prolonged (24 hr) infusions in the dog (16). There was no evidence of systematic changes in hepatic clearance over the time-course of the present study.

It is plain that lidocaine was not cleared by the lung in the "steady state" period. Extensive lung tissue uptake of lidocaine and other congeners has been reported to occur in vitro (17), and this has been re-

Table 2. Hemodynamic and Lidocaine Disposition Data in General Anesthesia Studies

Study	CO[a] (L/min)	Ca[a] (mg/L)	CL[a] (L/min)	ERh[a]	HBF[a] (L/min)	CLh[a] (L/min)	ERr[a]	RBF[a] (L/min)	CLr[a] (L/min)	CLiWS (L/min)	CLiPT (L/min)
Before lidocaine infusion during general anesthesia											
1	3.3 ± 0.2	—	—	—	1.49 ± 0.09	—	—	0.40 ± 0.01	—	—	—
2	3.6 ± 0.4	—	—	—	1.36 ± 0.30	—	—	0.58 ± 0.02	—	—	—
3	3.8 ± 0.2	—	—	—	1.01 ± 0.07	—	—	0.56 ± 0.01	—	—	—
4	3.6 ± 0.3	—	—	—	1.85 ± 0.46	—	—	0.74 ± 0.07	—	—	—
During lidocaine infusion during general anesthesia											
1	2.1 ± 0.7	3.9 ± 0.07	1.21	0.92 ± 0.03	0.53 ± 0.05	0.48 ± 0.05	0	0.20 ± 0.01	0	6.0	1.4
2	4.2 ± 0.2	5.6 ± 1.8	0.84	0.96 ± 0.02	1.22 ± 0.35	1.17 ± 0.29	0.17 ± 0.17	0.32 ± 0.02	0.06 ± 0.06	29	3.9
3	3.8 ± 0.5	3.9 ± 1.3	1.21	0.94 ± 0.02	1.46 ± 0.31	1.38 ± 0.28	0.26 ± 0.23	0.29 ± 0.02	0.08 ± 0.01	19	4.1
4	2.0 ± 0.3	3.1 ± 0.4	1.51	0.87 ± 0.04	0.90 ± 0.20	0.78 ± 0.17	0.24 ± 0.07	0.34 ± 0.05	0.08 ± 0.02	6.0	1.8

Abbreviations: CO, cardiac output; Ca, lidocaine arterial blood concentration; CL, lidocaine mean total body clearance; ERh, lidocaine hepatic extraction ratio; HBF, hepatic blood flow; CLh, lidocaine hepatic clearance; ERr, lidocaine renal extraction ratio; RBF, renal blood flow; CLr, lidocaine renal clearance; CLiWS, mean intrinsic hepatic clearance of lidocaine, "well-stirred" model; CLiPT, mean intrinsic hepatic clearance of lidocaine, "parallel tube" model.
[a] Values are mean ± SD.

lated to a first pass extraction after bolus injections in humans and pigs (18,19). This first pass lung uptake has the potential effect of reducing the peak concentrations of drug and delaying slightly its transmission into the systemic circulation and is, perhaps, instrumental in modulating some of the clinical effects of these drugs (20). However, the first pass lung extraction is a transient drug distribution effect—not a clearance—and is due to reversible binding related to the physicochemical properties of both the drug and local tissue (17). The present studies have made it plain that lung does not metabolize lidocaine in the sheep because there was no pulmonary arterial to aortic concentration gradient at steady state.

The renal clearance of lidocaine is uniformly low in mammals, including sheep (21), which has led to the generally held conclusion that lidocaine is eliminated from the body virtually exclusively by hepatic metabolism. This view has been supported by measurements of its oral bioavailability (22) and, on occasion, by direct observation of hepatic clearance (11). This study has provided an opportunity to examine this statement critically because both the mean total body clearance and the regional clearances were measured. Two comments would seem pertinent.

First, a low renal clearance of lidocaine relative to the total body clearance was confirmed, although its renal extraction ratio was higher than would have been predicted from reports of the fraction of dose excreted in urine (21). Thus it is possible that some of the renal extraction ratio represents some renal metabolism as well as excretion.

Second, there was a marked difference between the total body clearance and the directly measured hepatic clearance in two of each of the control-drug and general anesthesia studies. It has been noted by others that only 70% of lidocaine clearance in humans is hepatic (23), and propranolol, another drug commonly regarded as having synonymous total and hepatic clearances, also had a difference between hepatic and total clearances of similar magnitude to that of lidocaine (24). Thus, nonrenal clearance of drugs should not be regarded as hepatic clearance unless verified experimentally. Studies are presently underway to determine whether lidocaine is subject to extravisceral clearance or avid tissue binding (25).

In the present studies, there were no consistent effects of halothane anesthesia on the components of the hepatic clearance equation, although there were consistently lower values of renal and total body clearance. The mean hepatic blood flow was 23% less in the general anesthesia studies than in the control-drug studies, but the mean hepatic extraction ratio was 10% greater. The mean decrease in hepatic clear-

ance to 79% of the mean value in the control drug studies was not statistically significant.

Mean decreases in hepatic blood flow of 20–40% have been consistently observed in this preparation under halothane anesthesia (13). In general anesthesia studies 2 and 3 in which hepatic blood flows were not decreased, the mean arterial lidocaine concentrations were approximately 4 mg/L, i.e., twice those measured in the other two studies. Thus, although lidocaine did not systematically increase hepatic blood flow in the control-drug studies, it is possible that it opposed the effects of halothane in two of the general anesthesia studies, thus contributing to the observed variability in hepatic blood flow.

The changes in hepatic blood flow produced by inhalational anesthetic agents are complex. Recent studies performed in the dog, the pig, and the sheep have shown that halothane, enflurane, and isoflurane each reduce total hepatic blood flow in a dose-dependent manner (13,26–30). However, the relative changes in portal venous and hepatic arterial flows produced by the different agents are not consistent, even within the same species and using the same techniques of blood flow measurement. For example, Gelman et al., using the microsphere method for measurement of regional blood flow in the dog, found that portal flow was progressively reduced by 1 and 2 MAC halothane and isoflurane, whereas hepatic arterial flow was maintained at 1 MAC halothane, reduced at 2 MAC halothane, and was increased during isoflurane anesthesia (25,27). Indocyanine green clearance decreased progressively with increasing doses of halothane, but did not correlate with flow changes, suggesting that hepatic extraction ratios must have changed independently (27). From studies in the dog with electromagnetic flow probes, Hughes et al. reported that both enflurane and halothane decreased total hepatic blood flow to the same degree for equianesthetic concentrations. However, halothane decreased hepatic arterial blood flow to a greater extent than portal venous blood flow, and the reverse applied to enflurane (28). Therefore, different patterns of blood flow distribution occur with different agents. Each agent has the potential to reduce the clearance of drugs with "flow-limited" hepatic clearances (31), but the magnitude of the changes may vary in proportion to the changes in the distribution of the blood flow and the particular circumstances, some of which may oppose the changes.

In contrast to the unequivocal effects of halothane anesthesia on the clearances of a variety of other drugs studied in this preparation (i.e., diminished total body, renal, hepatic, and pulmonary clearances) (5,32–38), and to the effects on total body and renal clearances

in this study, the lack of dramatic effects on lidocaine hepatic clearance in this study was surprising. Thus, not only should data not be extrapolated from anesthetized to conscious animals or subjects, but it should also not be assumed that an anesthetic agent will produce similar effects on the disposition of drugs even those with similar chemical and pharmacologic properties.

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Plasma and Cerebrospinal Fluid Progesterone Concentrations in Pregnant and Nonpregnant Women

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DATTA S, HURLEY RJ, NAULTY JS, et al. Plasma and cerebrospinal fluid progesterone concentrations in pregnant and nonpregnant women. Anesth Analg 1986;65:950-4.

Pregnancy is associated with a wider dermatomal spread of local anesthetics after epidural and spinal anesthesia. This phenomenon also exists in the immediate postpartum period. The mechanism of this observation is unresolved. However, an increase in progesterone concentration in pregnancy has been implicated as one of the factors. Although plasma progesterone concentrations in humans have been well-documented, the cerebrospinal fluid (CSF) progesterone levels, which may also be important in this regard, have not been determined. Therefore, this study was undertaken to measure plasma and CSF progesterone in the nonpregnant, term parturient and in the immediate postpartum patient and also to determine the relationship between the CSF progesterone concentration and the intrathecal spread of lidocaine

used for spinal anesthesia. The plasma progesterone concentrations in 12 nonpregnant, 21 term and eight postpartum patients were 2.3 ± 61 (SEM) ng/ml, 122 ± 8 ng/ml and 16 ± 2.2 ng/ml, respectively. The CSF progesterone concentrations in term parturients (3 ± 0.28 (SEM) ng/ml) and postpartum patients (1.03 ± 0.16 ng/ml) were eight and three times greater than that of nonpregnant women (0.39 ± 0.01 ng/ml). Significantly less lidocaine was needed ($P < 0.05$) for comparable segmental levels of spinal anesthesia in term and postpartum patients than in nonpregnant individuals. These data suggest that high CSF, plasma progesterone concentrations, or both may augment the anesthetic spread of lidocaine.

Key Words: HORMONES—progesterone. ANESTHESIA—obstetric. ANESTHETIC TECHNIQUES—spinal. PREGNANCY—CSF and plasma progesterone levels.

Pregnancy is associated with an increased spread of local anesthetics so that less drug is required for a given level of epidural or spinal anesthesia (1,2). A wider dermatomal spread of local anesthetics after regional anesthesia has been reported in early and late pregnancy and immediately after delivery (1–4). The mechanism of this phenomenon is unclear. Factors that have been implicated include the following: 1) distention of epidural veins caused by obstruction of the aorta and vena cava by the gravid uterus re

sulting in decreased volume of epidural and spinal spaces (1,2); 2) an increase in progesterone concentration in pregnancy that may in turn alter the excitability of the central and peripheral nervous system (3,5–12); and 3) other biochemical changes that may alter neuronal responses to local anesthetics, e.g., an increased buffering capacity of CSF during pregnancy.

The plasma progesterone concentration of parturients is about 100 times that of nonpregnant women during the follicular phase of the menstrual cycle. We are unaware of any accurate measurement of CSF progesterone in women. We therefore measured total and protein-free fractions of progesterone in the plasma and CSF of nonpregnant patients, term parturients, and patients in the immediate postpartum period. We also determined the segmental dose requirement for intrathecal lidocaine used for spinal anesthesia in these three groups of patients. We hypothesized that CSF progesterone in direct contact with the spinal cord

Table 1. Plasma Progesterone Concentrations (ng/ml)

	Total	Bound	Free
Nonpregnant	2.3 ± 0.6^a (n = 12)	1.9 ± 0.7 (n = 7)	0.2 ± 0.1 (n = 7)
Pregnant	122 ± 8.0 (n = 21)	110 ± 11 (n = 18)	13 ± 1.2 (n = 18)
Postpartum	16 ± 2.2 (n = 8)	14 ± 2 (n = 8)	2 ± 0.6 (n = 8)

^{a}Mean ± SEM.

and spinal nerve roots may alter the excitability of the nervous system and that CSF progesterone concentrations would be inversely related to the amount of local anesthetic required to achieve a given segmental level of anesthesia.

Materials and Methods

The protocol was approved by the institutional review boards of the hospitals. Informed consent was obtained from all patients. Five milliliters of blood and 0.5 ml of CSF were withdrawn just before the administration of spinal anesthesia for surgery from 12 nonpregnant patients, 21 term parturients and eight postpartum patients. Spinal anesthesia was performed with a 26-gauge needle introduced through the third lumbar interspace. In all cases, local anesthetics were injected slowly, with the patients lying in the right lateral position. Immediately upon completion of the injection, the patients were placed in the supine position (term parturients with left uterine displacement). The spread of anesthesia was assessed by observing the highest level of loss of sensation (pinprick) at the midclavicular line 5, 10, and 15 min after the injection. Five percent hyperbaric lidocaine was used in eight nonpregnant patients, ten parturients, and nine postpartum patients (CSF progesterone was not measured in one postpartum patient). A mg/segment anesthetic value was calculated by dividing the number of milligrams of lidocaine by the total number of dermatomal segments anesthetized. The remaining patients, four nonpregnant and 11 term parturients, received 1% tetracaine with 10% procaine in equal volumes for their surgical procedures in anticipation that the duration of their surgery would exceed the duration of lidocaine spinal anesthesia. These patients were included in the study solely for the measurement of plasma and CSF progesterone concentrations. We did not use the tetracaine/procaine solution for postpartum tubal ligation because of the prolonged duration of anesthesia associated with this anesthetic. Therefore, no data are presented for the levels of spinal anesthesia achieved in postpartum patients when tetracaine was employed.

Spinal anesthesia was administered to term par-

turients prior to elective cesarean section, 12–18 h after delivery to postpartum women prior to tubal ligation and to nonpregnant women prior to orthopedic surgery. All patients were without major health problems, and most nonpregnant patients were in the follicular phase of their menstrual cycle. No patient was taking oral contraceptives. Total and unbound plasma and CSF progesterone concentrations were assayed with a radioimmunoactivity technique (13). The coefficient of variations of all these methods do not exceed 12%. Differences between mean values were tested by Student's t-test. A P value of <0.05 was considered significant. Correlation of plasma to CSF progesterone concentrations was accomplished with linear correlation and regression analysis.

Results

Patients ranged in age from 18 to 38. The mean age of the three groups did not differ.

The mean plasma progesterone concentration in pregnant and postpartum patients (Table 1) was 60 (122 ± 8 ng/ml) (SEM) and seven (16 ± 2.2 ng/ml) (SEM) times higher than in nonpregnant women (2.3 ± 0.61 ng/ml) (SEM). Eight to 10 percent of the progesterone in plasma was unbound (Table 1). The CSF progesterone concentration (Table 2) was eight times higher in term pregnant patients (3.0 ± 0.28 ng/ml) and three times greater in immediate postpartum individuals (1.03 ± 0.16 ng/ml) than in nonpregnant women (0.39 ± 0.01 ng/ml). Thirty percent of the progesterone in CSF was unbound to protein (Table 2) in pregnant, postpartum, and nonpregnant patients. The ratios of the concentration of progesterone in plasma and in CSF were compared in the three groups of patients. The ratio was 40:1 in the term pregnant patients, 16:1 in the postpartum patients, and 6:1 in the nonpregnant patients. When the concentration of unbound progesterone was compared, the ratios between plasma and CSF decreased to 15:1 in pregnant patients, 6:1 in postpartum patients, and 2:1 in nonpregnant patients. There was no correlation between plasma and CSF progesterone concentrations in nonpregnant patients, whereas a highly significant correlation was observed in term

Table 2. CSF Progesterone Concentrations (ng/ml)

	Total	Bound	Free
Nonpregnant	0.39 ± 0.01[a] (n = 12)	0.26 ± 0.01 (n = 7)	0.11 ± 0.003 (n = 7)
Pregnant	3.0 ± 0.28 (n = 21)	1.68 ± 0.23 (n = 18)	0.85 ± 0.12 (n = 18)
Postpartum	1.03 ± 0.16 (n = 8)	0.70 ± 0.11 (n = 8)	0.33 ± 0.05 (n = 8)

[a]Mean ± SEM.
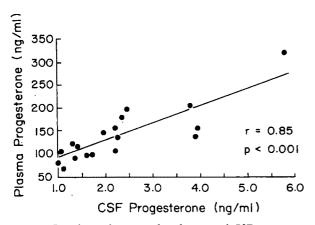
Figure 1. Correlation between the plasma and CSF progesterone (ng/ml) in term parturients (n = 18, r = 0.85, P < 0.001).
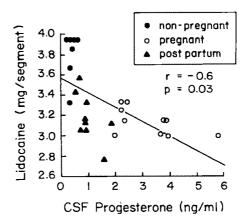
Figure 2. Correlation between the lidocaine dose requirement (mg/segment) and cerebrospinal fluid progesterone (ng/ml) in nonpregnant patients (n = 7), term parturients (n = 10), and postpartum patients (n = 9). r = −0.6, P = 0.03.

parturients (r = 0.85, P < 0.001) (Fig. 1) and postpartum patients (r = 0.78, P = 0.04). There was a significant correlation (Fig. 2) between lidocaine dose requirement for spinal anesthesia (mg/segment) and CSF progesterone concentration (ng/ml) (r = −0.6, P = 0.03). Significantly less lidocaine was required (P < 0.05) in parturients and postpartum patients than in nonpregnant patients (Table 3).

Discussion

This study has shown that the concentration of progesterone in CSF increases 8-fold in pregnancy and decreases in the immediate postpartum period. This implies a relatively rapid exchange of progesterone between blood and CSF. Sex hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) are carrier globulins for progesterone in plasma. The concentration of SHBG is much lower in CSF (14) than in peripheral blood. If CBG levels are similarly lower in CSF, this would result in a higher CSF concentration of unbound progesterone. Presumably unbound progesterone is the biologically active moiety. Indeed, in this study the percentage of unbound progesterone of 30% in CSF was three times greater than that in blood in pregnant postpartum and nonpregnant patients. Thus the gradient between unbound periph-

eral plasma progesterone and unbound CSF progesterone was 15 to 1 in term pregnancy, 6 to 1 in the immediate postpartum period, and 2 to 1 in nonpregnant patients. Therefore, the diffusion of progesterone from the plasma to the CNS compartment most likely is limited by the availability of CSF corticosteroid binding globulin. The mode of transport of progesterone from blood to CSF is not known at present. Diffusion through the choroid plexus is a possibility.

Our observation that the concentration of CSF and/or plasma progesterone in term pregnancy and in the immediate postpartum period is greater than in nonpregnant patients may explain the lower dose of anesthetics required in pregnant and postpartum patients than in nonpregnant patients. An interesting finding was that although the plasma and CSF progesterone concentration was three and eight times less, respectively, in postpartum patients than in term parturients, the segmental dose requirements for intrathecal lidocaine used for spinal anesthesia was the same in both of these groups. This suggests that a minimum level of progesterone in the CSF and/or plasma is necessary for this heightened local anesthetic activity.

It has been observed that less drug is required for given levels of epidural or spinal anesthesia during

Table 3. Lidocaine Requirement (mg/segment)

Nonpregnant	Pregnant	Postpartum
$n = 8$	$n = 10$	$n = 9$
3.80 ± 0.08^a	3.16 ± 0.04^b	3.21 ± 0.08^b

^{a}Mean $\pm$ SEM.
$^b P < 0.05$

pregnancy [1,2]. Bromage reported a wider dermatomal spread of epidural analgesia in pregnant patients and urged clinicians to use smaller doses of local anesthetics in parturients than in nonpregnant patients. Bromage's observation was confirmed by Hehre et al. [15]. Recently Fagareus et al. observed a wider dermatomal spread of local anesthetic drug in the epidural space as early as the first trimester of pregnancy [3]. They suggested that increased progesterone titers may play a role. Marx and Orkin compared the effects of equal doses of spinal anesthetic (tetracaine 5 mg–dextrose 50 mg) administered under identical conditions to obstetric and young gynecologic patients. They observed significantly more rapid onset, higher levels, and longer duration of blockade in the parturients [2]. Marx, in studying the level and duration of spinal analgesia in postpartum women undergoing tubal ligation, found a progressive decline in both height and duration of blockade over the first 3 days after delivery, indicating a gradual "wearing off" rather than an acute cessation of the altered response [4].

There is evidence in both animals and in human beings that progesterone can affect electrical excitability in the central and peripheral nervous system. As early as 1941 Selye showed the anesthetic effect of large doses of steroids administered to laboratory animals. Progesterone and pregnandione were particularly effective [16]. Later, Merryman et al. were able to induce sleep in pregnant women by injecting high doses of progesterone [17]. Progesterone has an anticonvulsive effect and raises the electroshock seizure threshold [5]. Progesterone can also prevent against induced convulsion [6]. The threshold of cortical EEG arousal on direct stimulation of the hypothalamus is greatly increased by progesterone [7]. Some clinical reports suggest that progesterone may ameliorate seizures [8]. Drury and Gold observed an increased threshold to painful stimulus in ovariectomized rats treated with progesterone [9]. Two other steroids, 5α-pregnane −3, 20 dione and 3α-hydroxy −5α pregnane −20 - one are derivatives of progesterone which also have hypnotic effects [10].

In 1982 we reported that bupivacaine (0.35 mM) produced a more rapid onset of conduction blockade in vagus nerve fibers isolated from pregnant rabbits

than in vagus nerve fibers isolated from nonpregnant rabbits [11]. We also reported an increased sensitivity to bupivacaine (0.1 mM–0.3 mM) in A and C rabbit vagus nerve fibers from pregnant animals [12]. We postulated that the increased plasma progesterone in pregnant animals might have been responsible for this observed difference. Although the exact mechanism of this progesterone effect is not clear, several factors may be involved: 1) a direct effect on membrane excitability; 2) an indirect action on neurotransmitters, or 3) an increased permeability of the neural sheath. The spinal cord and spinal nerves of our patients were exposed to elevated progesterone concentrations in both CSF and plasma. We postulate that the lesser amounts of lidocaine needed for comparable segmental levels of spinal anesthesia in term parturients and postpartum patients may somehow result from the interaction between plasma and/or CSF progesterone and these neuronal structures.

In summary, we observed significantly higher concentrations of progesterone in the plasma and CSF of term parturients and early postpartum patients when compared to nonpregnant patients; 30% of the CSF progesterone and 8% of the plasma progesterone remained unbound. This is important, because unbound fractions are considered to be physiologically active. We also observed a lower segmental dose requirement for intrathecal lidocaine used for spinal anesthesia in full term and immediate postpartum patients in comparison to nonpregnant patients. Although the exact mechanism is not known, high plasma and/or CSF progesterone may alter neuronal structure and be responsible for the enhanced anesthetic spread during epidural and spinal anesthesia in pregnancy.

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Neuropsychological Changes in a Young, Healthy Population after Controlled Hypotensive Anesthesia

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TOWNES BD, DIKMEN SS, BLEDSOE SW, HORNBEIN TF, MARTIN DC, JANESHESKI JA. Neuropsychological changes in a young, healthy population after controlled hypotensive anesthesia. Anesth Analg 1986;65:955–9.

We investigated the effect of controlled hypotension during halothane anesthesia on brain functions as measured by neuropsychological tests. Anesthesia in 17 patients included controlled hypotension, whereas in another 27 patients hypotension was not induced during surgery for correction of facial abnormalities. Intraoperative EEG recording showed no significant changes in EEG power during the induction of hypotension. Hypotensive anesthesia was not associated with greater postoperative impairment than normotensive anesthesia. Both groups did show short-term postoperative impairment of memory and learning. For at least the first 24 hrs after administration of a general anesthetic agent such as halothane, there is interference with consolidation of memory. This impairment was not apparent in follow-up examinations 6 months later.

Key Words: ANESTHETIC TECHNIQUES—hypotensive. PSYCHOLOGIC RESPONSES—postoperative.

Induced hypotension is a common adjunct to anesthesia used to diminish bleeding in order to reduce the volume of blood replacement and improve surgical technique by providing an essentially dry field during surgery. In spite of the use of this technique for more than four decades, the modest literature that presently exists concerning effects of hypotension upon patients' cognitive functioning is conflicting.

Eckenhoff et al. (1), in a study of patients undergoing elective plastic surgery with controlled hypotension, found no differences between nonsurgical control patients and postoperative surgical patients who had induced hypotension intraoperatively in tests of speed and accuracy of mental activity. In contrast, Gruvstad et al. (2) found greater postoperative impairment of intellectual tests in patients operated on with induced hypotension compared with those who did not have induced hypotension.

A similar conflict concerns the effect of halothane anesthesia upon performance on psychological tests. Bruce et al. found impairment of divided attention and memory tasks immediately after halothane anesthesia (3,4). According to Cook et al., the amnesic effect of halothane may be limited to verbal memory, with no effect upon visual memory (5). These adverse effects of halothane anesthesia have been found to persist for 2 hr on children's reasoning, motor, and memory functions (6), for 5 hr on adults' driving skills (7), for 2 days on adult subjects' memory and concentration (8), and for up to 8 days on healthy adult male subject's global intellectual functions (9). Other investigators, on the other hand, have found no adverse effects on memory after exposure to halothane (10,11) or upon driving skills of operating room nurses for up to 60 min after leaving the theater (12).

The goals of the present investigation were 1) to evaluate the general effects of anesthesia upon memory and cognition and to determine whether there are differential postoperative effects of hypotensive and normotensive halothane anesthesia upon neuropsychological tests, 2) to determine whether the intraoperative EEG correlates with postoperative changes in neuropsychological functioning, and 3) to ascertain whether or not such effects, if found, are permanent.

Methods

Subjects

All subjects were young, healthy white patients undergoing elective maxillofacial surgery at Univer-

sity Hospital, Seattle, Washington, between August 1980 and December 1981. Subjects in whom hypotensive anesthesia was used included 17 patients (5 males, 12 females) undergoing maxillary and mandibular osteotomies; the mean age was 26.2 yr. Subjects in the control group consisted of 27 patients (7 males, 20 females) undergoing sagittal mandibular osteotomies alone; the mean age was 29.3 yr. Duration of anesthesia averaged 192 min for the hypotensive group and 141 min for the normotensive group.

Anesthesia

In both groups anesthesia was induced with intravenous sodium thiopental (2–4 mg/kg) and maintained with halothane in oxygen. Over the course of the entire procedure, control subjects received on average 1.26% inspired halothane and maintained a mean arterial pressure (MAP) of 83.2 ± 14.0 (SD) mm Hg (Critikon Dinamap℗). During the initial 15 min of the procedures, subjects in the hypotensive group received on average 1.27% inspired halothane and maintained a MAP of 79.4 ± 17.2 mm Hg. Hypotension was induced with continuous intravenous administration of trimethaphan camsylate (Arfonad®, Roche) to achieve on average an MAP of 58.6 ± 3.1 mm Hg against a background of unchanged halothane delivery (1.33% inspired).

Electroencephalogram

Eight channels of EEG (International 10-20 system, parasagittal array) were recorded (Beckman Accutrace℗ 100A electroencephalograph) from 10 silver cup scalp electrodes, using an indifferent electrode. Recording bandpass was 0.15–75 Hz. Signals from all channels were stored on magnetic tape (Hewlett-Packard 3968A instrumentation recorder) and played back offline through 32 Hz-cutoff 7-pole lowpass Cauer elliptic filters (Frequency Devices 7438-f) into a digital computer (Digital Equipment Corp. PDP-15/30) for analysis and compression. Each channel of EEG was sampled at 128 Hz and the power spectral array computed for successive 4-sec epochs (13). Power coefficients (μV^2) were retained over the 0–32 Hz band. Ten successive spectra were obtained every 2.5 min for the duration of each case.

Psychological Testing

A battery of psychological tests was administered to each subject 24 hr prior to surgery, 24 hr after surgery, and again 6 months later. The vocabulary subtest of the Wechsler Adult Intelligence Scale (14) was chosen

as a measure of stored verbal learning, because stored verbal information is known to be relatively insensitive to changes in brain function. Performance on this test was expected to be robust, showing no effects of anesthesia. Measures of attention and general efficiency of information processing included the trail making test (15), digit vigilance, and visual search (16).

Memory functions were evaluated by means of the selective reminding test with an immediate and a 30-min delayed recall (17,18). Different forms of the test were administered in counterbalanced order at each of the evaluation periods. The selective reminding test (a multiple-trial, free-recall memory/learning procedure) analyzes storage, retention, and retrieval components of memory and learning of a verbal task. The subject is presented with a list of ten unrelated words, then tries to recall all of the words in the list. In successive learning trials the subject is selectively reminded only of those items he or she did not recall on the preceding trial. This procedure is continued throughout the learning of ten unrelated words until the entire list is recalled correctly on two successive trials or until ten trials have been given. Scores include total recall, the number of words recalled; long term storage, the number of words in long term storage; long term retrieval, the number of words retrieved from long term storage; and consistent long term retrieval, the number of words consistently retrieved from long term storage. The 30-min delay is the number of words recalled in one trial after a 30-min interval. All scores were computed across 10 trials.

In addition to the performance measures, self ratings of discomfort, grogginess, and anxiety were obtained on a 100-point scale. All tests were chosen with the following criteria in mind: 1) the necessity to sample different areas of functioning, 2) the need to minimize practice effects, and 3) sensitivity to alterations in brain functioning.

Statistical Tests

Change in scores (postsurgical minus presurgical) were computed for each of the neuropyschological variables. Differences between hypotensive and control groups were evaluated by means of t-test. Change in scores (6 month follow-up minus presurgical) for the total sample of 44 subjects were evaluated using the Wilcoxon signed-rank test.

Ten successive EEG power spectra obtained each 2.5 min were averaged and then broken into five contiguous frequency bands (1–4, 5–8, 9–15, 16–25, 26–32 Hz). In a selected EEG channel (F_3–C_3), power within each band was summed and was evaluated for vari-

Table 1. Mean and Standard Deviation of Scores on Psychological Tests for Normotensive and Hypotensive Groups Combined ($n = 44$)

	Preoperative	Postoperative (24 h)	Postoperative (6 months)
WAIS-vocabulary (Scale Score)	12.8 ± 2.3	12.4 ± 2.2	13.1 ± 2.9
Trails			
A (sec)	23.4 ± 6.0	21.7 ± 4.9	20.7 ± 5.8[a]
B (sec)	51.2 ± 16.8	50.2 ± 24.5	43.3 ± 13.1
Digit vigilance (sec)	86.2 ± 15.8	88.2 ± 21.3	80.4 ± 16.9[a]
Visual search (sec)	133.7 ± 55.1	117.9 ± 55.4	119.4 ± 50.3
Selective reminding test			
Total recall	90.6 ± 7.3	78.4 ± 15.3[a]	90.0 ± 10.0
Long term storage	89.7 ± 8.5	73.5 ± 20.7[a]	89.7 ± 9.6
Long term recall	87.8 ± 9.2	71.9 ± 18.4[a]	87.8 ± 11.9
Consistent long term retrieval	79.4 ± 19.8	68.0 ± 76.9[a]	82.5 ± 18.4
30-Min delay recall	8.6 ± 1.4	6.8 ± 2.5[a]	8.6 ± 1.3
Subjective ratings			
Discomfort	4.0 ± 9.7	41.9 ± 24.2[a]	7.2 ± 17.0
Grogginess	4.2 ± 9.9	29.3 ± 24.7[a]	5.2 ± 11.6
Anxiety	31.9 ± 26.8	14.9 ± 20.6[a]	7.2 ± 12.4[a]

All values are mean ± SD.
Abbreviation: WAIS, Wechsler adult intelligence scale.
[a]$P < 0.01$ (change from presurgical levels).

ability across time and, in the hypotensive cases, whether the total power in each band changed significantly between before and during hypotensive periods (paired t-test).

Results

The most remarkable feature of the power spectra of the EEG during these cases was the variability with time. Across all the hypotensive cases, the coefficients of variance of EEG power for the 1–4, 5–8, and 9–15 Hz bands before hypotension was induced were 88, 71 and 71%, respectively; during the hypotensive period they were 92, 85 and 100%, respectively. Similar variability was seen in patients in whom hypotension was not induced. Thus the lability of power in the EEG renders this mode of analysis insensitive to subtle changes in cerebral function under the conditions of our study. We found no significant change in EEG power in any band from the prehypotensive period during the period of induced hypotension.
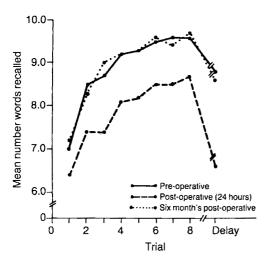
The neuropsychological test performance in the hypotensive and control groups was similar preoperatively. The data was analyzed, therefore, to answer the following questions:

Does induced hypotension during surgery affect postoperative performance? No significant differences were found between the hypotensive and normotensive groups in the immediate postoperative period. In this group of healthy young adults, hypotensive anesthesia did not

affect performance on tests sensitive to the integrity of brain function differently from normotensive anesthesia.

Are there any general effects of anesthesia upon postoperative performance and, if so, are they permanent? Scores for the two groups combined at each evaluation period are shown in Table 1. As expected, all subjects reported an increase in both discomfort and grogginess and a reduction in anxiety during the immediate postoperative period. However, the major findings from these analyses was a generalized effect of anesthesia upon learning and memory as measured by the selective reminding test. As can be seen in Table 1, subjects recalled significantly fewer words 24 hr after surgery. On a new list of ten words they cannot store new information in or retrieve information from long term storage as effectively. Fewer words are remembered after a 30-min interval.

In Figure 1 we show for both groups combined the mean number of words recalled on each trial of the selective reminding test before surgery, 24 hr after surgery, and 6 months later. The number of words recalled on the first trial does not differ significantly, implying that attention (span of attention or short-term memory) is similar at each evaluation period. However, during the immediate postanesthesia period on all subsequent trials, learning took place more slowly and information was not retained as effectively over a 30-min interval. These data suggest that halo-

Figure 1. Mean number of correct responses on consecutive trials of the selective reminding test at preoperative, postoperative, and 6-month follow-up periods for both groups combined (n = 44). Delay represents recall 30 min after the eighth trial.

thane anesthesia and surgery interfere with consolidation of memory in the immediate postoperative period.

As the results in Table 1 and Figure 1 suggest, subjects had returned to preoperative levels by the 6-month follow-up, indicating no permanent effects of the anesthesia. The modest improvement in the time required to complete trails A and digit vigilance tests in all likelihood represents minor practice effects. The further reduction in anxiety at 6 months was expected with full recovery from surgery.

Discussion

Use of hypotensive anesthesia was not associated in the present study with greater impairment on psychological tests than was observed in control subjects who did not receive hypotensive anesthesia. One major difference between the results reported by Gruvstad et al. (2), who found greater impairment among hypotensive patients compared with control patients, and the present results is the age of the subjects: 41.7 yr and 26.2 yr, respectively. Perhaps the potentially deleterious effect of a hypotensive agent upon brain functions increases with age. Also, all methods of inducing hypotension might not yield the same outcome. Conceivably, a differential influence of hypotension alone could have been observed if the hypotension had been induced by deep anesthesia or some other pharmacological agent.

Although controlled hypotension produced no specific detrimental effects on neuropsychological functioning, subjects in both groups experienced difficulties 24 hr after surgery, reflecting the effects of

halothane anesthesia. Of the mental processes examined, the effect appears to be specific to memory and learning. As expected, the ability to define words (i.e., vocabulary) was not altered. Because complex measures requiring speed, flexibility, and vigilance were not impaired, findings cannot be attributed to the effects of discomfort, grogginess or sleep loss. The halothane-induced deficit is relatively specific to storing new information into long term memory, retrieving the information that can be stored, and retention over time for later use. In other words, new material is learned more slowly, remembered less well, and forgotten more quickly. Our findings of problems with memory and learning after general anesthesia are consistent with those results reported by others in children (6) and adults (3,4) and support the conclusion of a primary effect of halothane anesthesia upon left hemisphere functions caused by a "deficit in the active verbal processes called into action during encoding and retrieval of verbal information" (19).

Our results suggest that patients undergoing halothane anesthesia should be advised to delay making any personal or professional decisions in the immediate postoperative period even if they are medically recovered to the point of being discharged from the hospital or ambulatory care center. They can, furthermore, be reassured that healthy young adults show full recovery by the eighth day after anesthesia and that there are no known long-term effects of halothane anesthesia (9). Comparisons of the effects of different general anesthetic agents upon postsurgical cognitive performance would determine which agents interfere least with postsurgical learning and memory and the time frame within which full recovery takes place.

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The Partial Pressure of Isoflurane or Halothane Does Not Affect Their Solubility in Rabbit Blood or Brain or Human Brain:

Inhaled Anesthetics Obey Henry's Law

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COBURN CM, EGER EI II. The partial pressure of isoflurane or halothane does not affect their solubility in rabbit blood or brain or human brain: Inhaled anesthetics obey Henry's Law. Anesth Analg 1986;65:960-2.

We tested the possibility that the solubility of halothane or isoflurane in rabbit blood or human or rabbit brain does not obey Henry's Law. We measured the blood/gas and brain/gas partition coefficients for both anesthetics at approximately

1 MAC and at 0.01 MAC at 37°C. The partition coefficients determined at the high vs low partial pressures did not differ. We conclude that the solution of isoflurane and halothane in blood and brain obeys Henry's Law.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane. SOLUBILITY—halothane, isoflurane. PHYSICS—Henry's law.

Using nuclear magnetic resonance, Wyrwicz et al. observed the washin and elimination of halothane and isoflurane in the brains of rabbits (1,2). They found that cerebral elimination of anesthetic was slower than previously observed by others (3). Their findings also conflict with what would be predicted if one assumes that elimination is limited solely by anesthetic solubility in brain, cerebral blood flow, and elimination at the lungs (4).

We previously postulated that these data might be explained by changes in anesthetic solubility in blood at low vs high partial pressures (5). Most studies of solubility apply anesthetic partial pressures near MAC and may underestimate solubility, especially if saturable binding sites are present at the lower partial pressures obtained during anesthetic elimination. Binding sites in blood and muscle are known to exist for xenon (6) and cyclopropane (7,8). If there are binding sites in blood for halothane and isoflurane, the solubility of these anesthetics might be considerably higher at the lower partial pressures accompanying elimination. However, in human blood, we found no evidence of saturable binding sites for either agent (5).

We also suggested that the data of Wyrwicz et al. could be explained by differences between human and rabbit blood, or by the presence of binding sites in brain rather than in blood. Binding sites in the brain are known to exist for narcotics (9), benzodiazepines (10), and barbiturates (11). In this report, we have tested the possibility that isoflurane or halothane solubility is greater at decreased partial pressures in rabbit blood, or at decreased partial pressures in rabbit or human brain.

Methods

With the approval of the University of California Committee on Human Research, brain tissue (frontal lobe) was obtained at autopsy of patients who died from diseases that did not immediately affect the brain. The dura was removed from each specimen, and the volume of the specimen was determined by displacement in a premeasured volume of saline. The approximately equal volumes of brain and saline were then homogenized with a Kinematic CH-6010 homogenizer. Four 30-ml syringes were prepared by lubricating the barrels with silicone grease. Approximately 13 ml of homogenate was added to each syringe.

Two of the samples prepared in this manner were then equilibrated with a partial pressure of isoflurane or halothane at approximately 1 MAC, and the other two with a partial pressure of approximately 0.01 MAC. To achieve the above partial pressures we added about 13 ml of halothane in air or isoflurane in air from

Table 1. Partition Coefficients for Isoflurane and Halothane at 1 MAC and 0.01 MAC in Human and Rabbit Brain and Rabbit Blood[a]

	Human Brain		Rabbit Brain		Rabbit Blood	
	High[b]	Low[c]	High[b]	Low[c]	High[b]	Low[c]
Isoflurane						
n	4	4	8	6	6	5
% Anesthetic	1.00 = 0.01	0.0106 ± 0.0013	1.02 ± 0.05	0.0114 ± 0.0006	0.88 ± 0.08	0.0089 ± 0.0008
Tissue/gas partition coefficient	2.39 = 0.09	2.50 ± 0.17	2.29 ± 0.16	2.30 ± 0.08	1.59 ± 0.18	1.73 ± 0.17
Halothane						
n	5	5	8	6	6	6
% Anesthetic	0.52 ± 0.03	0.0045 ± 0.0005	0.51 ± 0.04	0.0049 ± 0.0007	0.39 ± 0.03	0.0037 ± 0.0003
Tissue/gas partition coefficient	5.14 ± 0.49	5.39 ± 0.18	4.89 ± 0.41	5.22 ± 0.59	4.36 ± 0.53	4.36 ± 0.60

[a]All values are means ± SD.
[b]High, high concentration.
[c]Low, low concentration.

previously prepared tanks having the requisite partial pressures. The syringes were shaken and the gaseous portion discharged. This procedure was repeated twice for halothane and once for isoflurane. After the final addition of gas, the homogenate–gas mixture was placed in a tonometer (in a waterbath at 37°C) and allowed to equilibrate for 2 hr. Every 15 min during the period of equilibration, the syringes were removed from the water bath and shaken vigorously for about 30 sec.

After 2 hr, the concentration of the gas phase was measured by gas chromatography. Nitrogen was used as the carrier gas at a flow rate of 40 ml/min. Each channel of the chromatograph contained an $\frac{1}{8}$-inch column packed with 10% SF-96 Chromosorb WHP 60/80 mesh and a flame ionization detector with an air–hydrogen gas mixture (flow rates of 283 and 40 ml/min, respectively). The temperature in both columns was set to 75°C.

An aliquot (approximately 10 ml) of the homogenate was injected into an evacuated (approximately $\frac{1}{3}$ atmosphere) flask of precisely known volume (approximately 600 ml). The flask was placed in the waterbath and warmed to 37°C before it was equilibrated with ambient pressure. The flask was maintained in the water bath for 1 hour and was shaken vigorously at 15-min intervals. At the end of the period, 30 ml of air was added to the flask and barbotaged 8–10 times. This mixture was then analyzed by gas chromatography.

The homogenate/gas partition coefficient (HG) was calculated as follows:

$$[(Vf + 30 \text{ ml} - Vh)/Vh] \, [Cf/(Cs - Cf)]$$

where Vf is the premeasured volume of the flask; Vh is the volume of the aliquot of homogenate; Cf is the

concentration in the flask; and Cs is the concentration in the syringe. The brain/gas partition coefficient (BG) was calculated as follows:

$$[(Vh) \, (HG) - (Vs) \, (SG)]/Vb$$

where Vs is the volume of the saline in the aliquot of homogenate; SG is the saline/gas partition coefficient (5); and Vb is the volume of brain in the aliquot of homogenate.

We also determined the brain/gas and blood/gas partition coefficients for rabbit tissue. White New Zealand male rabbits weighing 2–2.5 kg were killed by inhalation of 100% carbon dioxide. Blood was removed into a 30-ml syringe and anticoagulated with EDTA. The partition coefficients for blood were determined as in our previous study (5). The brain was excised and the dura removed. The brains from groups of five rabbits were pooled and treated using the same methods applied to human tissue.

We compared the results at high vs low concentrations with both paired and unpaired t-tests. Unpaired tests were applied to the results of rabbit blood because there was not pairing of these specimens. Paired analysis was performed for the human samples for which both determinations (high and low partial pressures) were completed. Paired and unpaired analyses were performed for the comparisons of results for rabbit brains. We considered a P value of less than 0.05 significant. All values obtained were means ± SD.

Results

We found no significant difference in the solubility of halothane or isoflurane in human brain at high vs low partial pressures (Table 1). Similarly, no significant difference was found in rabbit blood or brain.

Discussion

The values we obtained for anesthetic solubility in whole human brain are comparable to those previously determined by others. Our value of 5.14 ± 0.49 for halothane at an anesthetizing partial pressure is similar to that of 4.82 ± 0.20 reported by Lerman et al. (12), and slightly lower than that of 6.0 ± 0.3 obtained by Larson et al. (13). Similarly, our value of 2.39 ± 0.09 for isoflurane compares well with that found by Lerman et al., 2.36 ± 0.08 (12). The values we obtained for solubility in rabbit brain did not differ from those for solubility in human brain (Table 1).

Our values for solubility in rabbit blood are higher than those we found previously for human blood (5). Our value for halothane in rabbit blood was 4.36 ± 0.53, whereas the value in human blood was 2.62 ± 0.27. Similarly, our value for isoflurane in rabbit blood was 1.59 ± 0.18, and the value in human blood, 1.51 ± 0.09. These findings are consistent with previous reports of greater anesthetic solubility in rodent blood. For example, a value of 6.56 ± 0.17 was determined for halothane in rat blood by Wahrenbrock et al. (14).

Over the range of anesthetic partial pressures studied in blood, we found no evidence of saturable binding sites. We conclude that Henry's law is obeyed in this range of partial pressures. If binding sites exist, they must be saturable at much higher or lower partial pressures, or be too few in number to be detected by our analyses.

Our results do not explain the finding of Wyrwicz et al. of a prolonged residence of isoflurane and halothane in rabbit brain. Two explanations for their findings remain. One possibility is that there are variations in solubility within the brain, and that Wyrwicz et al. were measuring the washout from a part of the brain with a high affinity for anesthetic. Similarly, there may be areas of low perfusion that produce prolonged time constants. A second possibility is that the nuclear magnetic resonance measurements made by Wyrwicz et al. may not accurately reflect events in the brain. For example, they may make no dis-

tinction between the brain and the tissues overlying it, and anesthetic elimination from these tissues may have a long time constant.

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Review Article

Pharmacologic and Clinical Aspects of Preoperative Medication

Paul F. White, PhD, MD

Preoperative medication is dominated by tradition. As Beecher remarked more than 20 years ago, "empirical procedures firmly entrenched in the habits of good doctors seem to have a vigor and life, not to say immortality of their own (1)." Much of the rationale for preoperative medication arose in the days when the most widely used anesthetics were ether and cyclopropane. In order to minimize the side effects of these drugs, anesthetists sought to bring patients to the operating room heavily sedated with a very dry mouth. Today the most common reason for administering premedication is to make the experience of anesthesia and surgery more pleasant and less traumatic for our patients.

Based on one's own clinical experience and favorite routine, an anesthetist may order a sedative-hypnotic, narcotic analgesic, major tranquilizer, or anticholinergic drug. Frequently, a combination of two or more compounds from different drug groups is prescribed. An important reason for the use of so many different drugs and combinations is that there is no general agreement about the indications for premedication. It is generally accepted that patient apprehension (or anxiety) is a major factor that should be controlled in the preoperative period. The incidence of clinically significant anxiety in patients awaiting a surgical operation has been variously reported to range from 40 to 80%. The incidence is higher in women than men (in particular, women weighing less than 70 kg) and in all patients previously or currently on sedative medication (2). The most frequent causes of preoperative anxiety relate to patients' concern about their

general health, the operation, leaving their family, uncertainty regarding the future, anesthesia, and the fear of postoperative discomfort.

Psychologic Preparation

The psychologic component of preoperative preparation is provided largely by the anesthetist's visit and interview. Even a brief description of the anesthetic management plans and the events the patient should anticipate during the perioperative period serves to allay the natural fear that most individuals have of losing consciousness. In 1963, Egbert et al. evaluated the psychologic effects of the preoperative visit compared to pentobarbital, 2 mg/kg intramuscularly (IM) (3). Patients who had been visited by an anesthetist before surgery were significantly more likely to be calm on the day of the operation (Table 1). If the primary purpose of the premedication is to allay anxiety, these data suggest that pentobarbital is relatively ineffective. More recently, Leigh et al. reported that anxiety levels in patients who received preoperative reassurance about anesthesia from an anesthetist were significantly lower than those in a control group given no support (4). Furthermore, these authors reported that a booklet specially written to reassure the patient about anesthesia was significantly less effective than the personal interview in decreasing anxiety.

Although a preoperative visit by the anesthetist clearly lessens anxiety, premedication is widely used to allay patient fears for those events over which the anesthetist has less influence. In addition, premedicant drugs are used to minimize pain, to produce amnesia and sedation, to decrease salivary and gastric secretions, to prevent nausea and vomiting, to provide for prophylaxis against allergic reactions, to decrease the amount of anesthetic drug required for the surgical procedure, and to suppress reflex responses to the surgical stimulus. In this article, the important pharmacologic properties of the major premedicant

Table 1. Comparison of Psychologic Effects of
Preoperative Interview and Pentobarbital, 2 mg/kg IM[a]

Treatment group	Percentage of patients		
	Apprehensive	Sedated	Suitable for surgery
Control	58	18	35
Pentobarbital	61	30[b]	48
Interview	40[b]	26	65[b]
Combination	38[b]	38[b]	71[b]

[a]From Egbert et al. (3).
[b]Significantly different from control, $P < 0.05$.
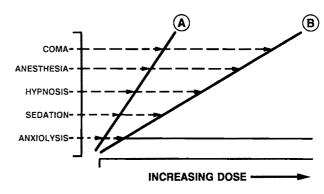
drug groups are discussed, and some of the comparative pharmacologic studies that have appeared in the medical literature over the last two to three decades are reviewed.

Pharmacologic Preparation

The rational use of premedicant drugs may allow the patient to enter the operating room suite with a minimum degree of apprehension, sedated but easily arousable and cooperative without uncomfortable side effects. From the patient's point of view, lack of recall (or amnesia) and relief of anxiety (or anxiolysis) are the primary objectives of preoperative medication. However, most patients do not want prolonged amnesia (i.e., they want to be able to recall events both before and after the operation) (5). In fact, excessive sedation and prolonged amnesia may actually increase anxiety.

Almost as critical as the drugs themselves is the time and route of administration of the premedicant relative to the patient's arrival in the operating room. Most orally administered premedicants should be given 60–90 min prior to the patient's arrival in the operating room to exert their full effects. Even intramuscular premedicants require 30–60 min to achieve peak effects. The timing of preoperative medication was recently evaluated in a prospective study at Stanford (Forrest WH; personal communication). This study revealed that 69% of patients arrived 30–90 min after receiving their premedication, and the remaining 31% arrived within 30 min after administration of their premedication. The major reason that the preoperative medication was not administered at the optimal time was due to late premedication requests from operating room personnel to nursing personnel on the surgical ward.

Before reviewing the comparative pharmacology of the major premedicant drug groups, it is useful to consider some of the common pitfalls of many of the comparative premedicant drug studies. Often only one dose of each drug is studied, and therefore it is

Figure 1. Spectrum of central nervous system activity. Sedative-hypnotic compounds produce a dose-dependent spectrum of CNS depression. In this schematic, drug A might represent a barbiturate (e.g., pentobarbital), whereas drug B might represent a benzodiazepine (e.g., diazepam).

impossible to know whether "optimal" doses were compared. Furthermore, study drugs are frequently given in combination with other centrally active drugs. Variability is increased when drugs given orally or intramuscularly are compared to drugs given by the intravenous (IV) route. More important, the time–effect relationships may differ for the various study medications, making it difficult to interpret the results of a study when all observations are recorded at the same time interval. Finally, the responses evaluated are frequently subjective and can be misinterpreted by an observer (6). For example, the ability of a drug like droperidol to induce a state of drowsiness or sedation does not ensure relief of anxiety. In fact, Forrest et al. found that none of the six intramuscular premedicants they studied had a significant effect upon the patient's level of preoperative anxiety, although the nurse observer's ratings frequently revealed dose-dependent sedation and decreases in apprehension (7). Thus even though routinely prescribed premedicants can make patients drowsy, this does not necessarily correlate with anxiety relief. These data also emphasize the difficulty in quantitatively assessing subjective responses such as anxiety. After reviewing many of the premedicant studies that have appeared in the anesthesia literature over the last 25 years, I have to agree with Forrest et al. that "most clinical investigations of the efficacies of specific (premedicant) drugs have lacked both definition and persuasiveness (7)."

Sedative-Hypnotics and Tranquilizers

The most popular premedicants belong to the sedative-hypnotic group of drugs, which includes both the benzodiazepines and the barbiturates. All sedative-

Table 2. Intravenous Diazepam as a
Surgical Premedicant[a]

Dose (mg)	Anxiolysis[b]	Sedation[b]	Amnesia (%)[c]	Patient acceptance[d]
2.5	0.66	0.36	0	1.32
5	1.28	1.08	3	1.56
10	2.34	1.98	12	1.94
20	2.91	2.92	38	2.35

[a]From Conner et al. (13).
[b]Average change from baseline: −4 (worse) to +4 (improved).
[c]Patients failing to recall memory card.
[d]Mean scaled score: 0 (poor) to 3 (excellent).
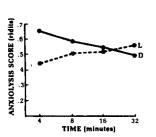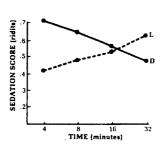
hypnotics produce a similar dose-dependent spectrum of central nervous system (CNS) activity. Although the slopes of their individual dose–response curves may differ, all drugs in this group produce a similar pattern of CNS depression (Fig. 1). Secobarbital and pentobarbital were widely used premedicants because of their ability to produce sedation without significant cardiorespiratory depression. However, these barbiturates have become less popular over the last 10–20 years with the widespread use of benzodiazepines (8). Comparative studies have indicated that benzodiazepines are more effective in producing anxiolysis and amnesia and are associated with higher patient acceptance than the barbiturates (9–11). For many years, chloral hydrate, triclofos, and the barbiturate compounds were the most popular nighttime hypnotics. More recent data indicate that the benzodiazepines (e.g., flurazepam, triazolam, lorazepam) (12) may also be superior to the barbiturates as hypnotics on the evening prior to surgery.

Diazepam, the prototypic benzodiazepine, produces dose-dependent anxiolysis, sedation, and amnesia (Table 2) (13). How does diazepam compare to lorazepam? In a study comparing orally administered diazepam, 0.1 mg/kg, and lorazepam, 0.05 mg/kg, Reynolds et al. (Anesth Rev 1982;9:17–21) reported that diazepam was significantly more effective in relieving preoperative anxiety. Although both drugs appear to produce comparable degrees of anxiolysis, sedation, amnesia, and patient acceptance after intravenous injection, diazepam is associated with a higher incidence of pain on injection and phlebitis, whereas lorazepam is associated with a more prolonged recovery time (14,15). However, the most important differences between these two benzodiazepines are not their qualitative pharmacologic differences, but rather the important differences in their time–effect relationships (Fig. 2). In the study by Conner et al. (14), the CNS effects of diazepam became apparent promptly after an intravenous bolus injection and then decreased over the subsequent 30 min.

In contrast, the CNS effects of intravenous lorazepam progressively increased over the same time interval. Other investigators have also reported more profound and more prolonged sedation and amnesia with lorazepam (vs diazepam) (15,16). The reasons for these differences may relate in part to their differing lipid solubilities. In addition, recent ex vivo receptor binding studies have also revealed higher association and dissociation rate constants at the benzodiazepine receptor for diazepam compared to lorazepam (17). Thus even though diazepam has a longer elimination half-life than lorazepam (20–40 hr vs 10–15 hr), its duration of clinical effects may be shorter because it dissociates more rapidly from the benzodiazepine receptor and is readily redistributed from vessel-rich tissues to lean muscle tissue. Whereas diazepam's principal metabolite (desmethyldiazepam) retains some pharmacologic activity and possesses a long elimination half-life (90–100 hr), lorazepam is metabolized to inactive metabolites. Furthermore, in contrast to diazepam, lorazepam's disposition and elimination is only minimally affected by liver dysfunction and aging (18–20). Nevertheless, dosages of all benzodiazepines should be decreased in the elderly because these patients may display enhanced sensitivity to the CNS depressant effects of these compounds.

Midazolam is a water-soluble benzodiazepine (Fig. 3) with a short elimination half-life (2–4 hr) that was recently approved for clinical use (21). Midazolam is approximately twice as potent as diazepam with respect to its sedative and anxiolytic properties. Its water solubility obviates the need for a solubilizing agent (propylene glycol) that can produce venoirritation and interfere with absorption after intramuscular administration, as seen with diazepam. Because of its rapid onset of sedative-anxiolytic effect and low incidence of postoperative side effects, midazolam appears to be an excellent intramuscular premedicant for pediatric patients (22). In addition, midazolam's short elimination half-life decreases its potential for accumulation after multiple doses (23). Midazolam is rapidly metabolized by hepatic microsomal enzymes to form inactive hydroxylated metabolites. Analogous to diazepam, midazolam's clearance rate may be decreased in elderly patients, resulting in a longer elimination half-life (24). Early clinical studies indicate that midazolam (0.08 mg/kg IM) may offer clinical advantages over other available sedative-anxiolytic drugs (25,26). Intramuscular midazolam was recently reported to produce a more rapid onset of action (peak effect at 30–45 min), more profound sedative and amnesic effects, and a more rapid recovery than diazepam (27). However, others have suggested that midazolam offers no advantage over diazepam in terms
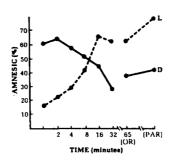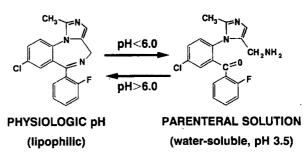
Figure 2. Comparative sedative, anxiolytic, and amnesic effects of diazepam (D), 20 mg IV, and lorazepam (L), 4 mg IV (14). The ridit scores are based on a reference population (mean score of 0.5). The higher ridit scores for all variables indicates a greater drug effect.

of speed of recovery of psychomotor function (28). Although midazolam is a potent sleep-inducing agent, its short duration of action may limit its use as a night-time hypnotic (29).

In comparing the sedative-hypnotics to the major tranquilizing drugs (phenothiazines and butyrophenones), the only pharmacologic property clearly shared by the two drug groups is sedation. Although arousability after higher doses of antipsychotic tranquilizers is usually easier than with the sedative-hypnotics, the global sedation produced by tranquilizers has frequently been described by patients as an unpleasant state of inner restlessness associated with the inability to express their feelings. As a result of its psychomimetic effects, premedication with droperidol may lead to refusal of surgery (30,31). Interestingly, observers and physicians may easily mistake the patient's outward appearance of calmness for mental tranquility. This apparent discrepancy between what the patient experiences and what the observer notes was demonstrated in a study by Herr et al. comparing diazepam and droperidol (32). Patient acceptance scores for diazepam were significantly higher than the physician scores, in contrast to droperidol, where the physician scores were higher than the patient scores.

Droperidol is a butyrophenone with prominent stimulant effects that remains a popular premedicant because of its potent antiemetic activity. Obese patients, patients undergoing opthalmologic and abortion procedures, patients receiving narcotic analgesics or etomidate, as well as those with a history of nausea and vomiting after a previous anesthetic often benefit from droperidol premedication. Low-dose droperidol (1.25–2.5 mg IV) has been shown to be effective in preventing postoperative nausea and vomiting (33,34). Droperidol can also produce unwanted extrapyramidal symptoms secondary to its dopaminergic receptor-blocking properties (35). Other antipsychotic

PHYSIOLOGIC pH
(lipophilic)

PARENTERAL SOLUTION
(water-soluble, pH 3.5)

Figure 3. Effect of pH on the chemical structure of midazolam, a new water-soluble benzodiazepine with anxiolytic, sedative, amnestic, and hypnotic properties.

tranquilizers that can be used for premedication include perphenazine, promazine and promethazine.

Hydroxyzine is a unique nonphenothiazine (antihistamine) tranquilizer with mild CNS depressant properties. Hydroxyzine possesses a wide spectrum of pharmacologic activity including anxiolysis, sedation, and analgesia, as well as antihistaminic (H_1-blocker), antiemetic, bronchodilating, and anticholinergic actions. Although hydroxyzine has not received official approval from the Food and Drug Administration for intravenous use, Wender et al. compared intravenous hydroxyzine and diazepam as surgical premedicants (36). Diazepam provided somewhat better anxiolysis, sedation, and patient acceptance, but its major advantage over hydroxyzine was its ability to produce amnesia. Oral diazepam, 0.1 mg/kg, was significantly more effective than an intramuscular combination of hydroxyzine, 1 mg/kg, and meperidine, 1 mg/kg, in relieving preoperative anxiety (Reynolds et al., Anesth Rev 1982;9:17–21). Intramuscular lorazepam, 0.05 mg/kg, produced a longer duration of sedation, a more profound effect on recall, and higher patient acceptance than intramuscular hydroxyzine, 1.5 mg/kg, for surgical premedication (37). Although the analgesic effectiveness of hydroxyzine is limited (38), when used in combination with morphine the two analgesics appear to be more efficacious than either drug alone (39). Interestingly, in a recent study comparing droperidol and hydroxyzine as pro-

Table 3. Effect of Premedicants on the Minimum Alveolar Concentration (MAC) of Anesthetic Agents

Premedicant (dosage)	Anesthetic (reference)	Decrease in MAC (%)
Diazepam		
0.2–0.4 mg/kg IV	Halothane (111)	35–44
0.5 mg/kg IV	Halothane (43)	36
Hydroxyzine		
2 mg/kg IV	Halothane (43)	22
Midazolam		
0.1–0.6 mg/kg IV	Halothane (112)	5–30
Morphine sulfate		
8–15 mg subcutaneously	Halothane (41)	7
10–15 mg IM	Fluroxene (42)	20
Pentazocine		
0.2 mg/kg IV	Halothane (43)	33

phylactic antiemetics, hydroxyzine was found to be significantly more effective at doses that produced comparable degrees of postoperative sedation and similar recovery times (40).
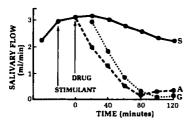
Narcotic (Opioid) Analgesics
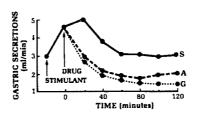
In the past, narcotics have been prescribed for premedication in an effort to facilitate the induction of anesthesia and to decrease the inhaled anesthetic requirement. The ability of opioid analgesics to decrease the anesthetic requirement is probably of little clinical significance (Table 3) (41–43). In fact, the routine use of narcotic analgesics as part of a premedicant regimen has been questioned by many investigators. Cohen and Beecher (44) stated many years ago that "unless there is pain, there is no need for a narcotic in preanesthetic medication." Interestingly, when morphine sulfate is given alone it produces some degree of dysphoria in up to 80% of pain-free patients and euphoria in only 10% (1). For patients in pain or dependent on narcotic analgesics, the situation is obviously quite different. The major problem associated with the use of narcotic analgesics relates to their high incidence of side effects (including nausea, retching, dizziness, flushing, respiratory depression, chest tightness, and occasional agitation). Morphine premedication significantly increases end-tidal carbon dioxide tension and decreases the ventilatory response to carbon dioxide (45). The agonist–antagonist analgesics (e.g., nalbuphine) may be associated with a lower incidence of postoperative side effects than the opioid compounds when used for premedication (46). Many drugs have been administered with the opioid analgesics in an effort to decrease their side effects. For example, droperidol decreases the incidence of nausea and vomiting associated with nar-

cotics, though it may not enhance the overall patient acceptability of narcotics (47). The centrally active anticholinergic scopolamine may enhance the anxiolysis, sedation, and amnesia produced by narcotic analgesics (48). Unfortunately, scopolamine does not decrease the side effects of morphine.
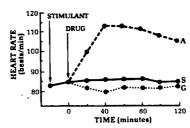
The sedative-narcotic combinations are probably of more clinical importance to practicing anesthesiologists. Because pain results in increased anxiety and anxiety exacerbates pain (49), combinations of sedative-anxiolytics and narcotics may act synergistically. Numerous anecdotal reports have alleged to demonstrate an additive (or supraadditive) action between narcotics and sedatives in terms of their analgesic effectiveness. Promethazine, a widely used phenothiazine, improves the relief of anxiety and the level of sedation as well as patient acceptance when added to morphine premedication (50). Although promethazine markedly increases the sedative effects of meperidine, it does not appear to "potentiate" meperidine's analgesic action (51). Interestingly, Hupert et al. showed that analgesia obtained when morphine was combined with hydroxyzine was significantly better than that obtained with morphine alone (52). As expected, drowsiness was significantly more frequent after the combination. Because the combination of hydroxyzine and morphine was a more effective analgesic than either drug alone, this combination might be expected to produce less respiratory depression than an equianalgesic dose of narcotic only.

Anticholinergics

The use of anticholinergic compounds as part of routine preanesthetic medication stems mainly from their antisialagogue and vagolytic actions (53). Although these investigators argued that the routine use of anticholinergic drugs for premedication is unnecessary, many practicing anesthetists still routinely use anticholinergic drugs. Secretions are troublesome only if they are excessive and interfere with the smooth conduct of anesthesia. Falick and Smiler evaluated the effects of glycopyrrolate on the anesthetic conditions in patients undergoing minor procedures and reported that 98% of the "unsatisfactory" ratings were related to excessive secretions and problems precipitated by secretions (e.g., laryngospasm, coughing) (54). How does glycopyrrolate, a noncentrally active drug, compare to atropine in terms of its peripheral anticholinergic effects? Glycopyrrolate, 0.2 mg IM, was similar to atropine, 1.5 mg IM, in decreasing salivary flow and gastric secretions (Fig. 4) (55). In contrast to atropine, glycopyrrolate did not significantly increase

Figure 4. Comparative effects of atropine (A), 1.5 mg IM, and glycopyrrolate (G), 0.2 mg IM (vs saline (S) control) on salivary flow, gastric secretions, and heart rate (55).

the heart rate. Neither drug is particularly effective in altering the gastric fluid pH or volume (56). Preoperative administration of glycopyrrolate, 4–5 µg/kg IM, did not significantly decrease the percentage of patients "at risk" to aspiration pneumonitis (gastric fluid pH < 2.5 and volume > 0.4 ml/kg) (57). Finally, recovery from anesthesia may be more rapid with glycopyrrolate than with atropine because glycopyrrolate's ionized (quaternary ammonium) structure decreases its ability to cross the blood–brain barrier.

• The other centrally-active anticholinergic, scopolamine, is eight to ten times more potent than atropine in terms of its effects on the CNS and significantly less potent than atropine in terms of its peripheral autonomic effects (58). Recent studies with transdermally-administered scopolamine, 1.5 mg over 72 hr, indicate that it may be an effective premedicant as a result of its sedative, antisialagogue, and antiemetic properties (59). Unfortunately, an excessive dose of scopolamine can also produce a syndrome associated with delirium, restlessness, confused speech, hallucinations, and prolonged somnolence (coma) after anesthesia, the so-called "central anticholinergic syndrome." Other side effects common to all anticholinergics include relaxation of the lower esophageal sphincter (60), mydriasis and cycloplegia (61), increases in respiratory dead space (45), and elevations in body temperature (58). Physostigmine, a centrally-active cholinesterase inhibitor, is effective in reversing the residual postoperative sedative effects of atropine and scopolamine (62).

Histamine H₂-Receptor Antagonists

Antacids, anticholinergics, gastrokinetic agents, and more recently, the H₂-blocking drugs have been administered preoperatively to patients considered to be at increased risk to aspiration pneumonitis. Theoretically, patients with a decreased level of consciousness, abnormal swallowing mechanism or disturbed gastrointestinal motility, or with a "full stomach"

would benefit from the prophylactic use of these agents. Obese patients might also benefit from preoperative administration of antisecretory drugs (63). The use of H₂-receptor antagonists can increase gastric fluid pH during the preoperative period by producing dose-related decreases in basal and nocturnal gastric acid production (64). In general, multiple dose regimens (e.g., a nighttime dose on the evening prior to surgery and a morning dose on the day of surgery) are more effective than single dose regimens in decreasing gastric acidity and volume. Parenteral administration is more effective than oral when a rapid onset of effect is desired (65).

Both of the commonly used H₂-receptor antagonists, cimetidine, 150–300 mg, and ranitidine, 50–100 mg, significantly increase gastric fluid pH within 1 hr after parenteral administration (66,67). Although these drugs are capable of decreasing the number of patients "at risk" for acid aspiration, neither drug completely eliminates this risk. Thus the use of an H₂-blocking drug does not obviate the need for careful anesthetic techniques to protect the airway during induction of anesthesia. In addition, cimetidine is capable of inhibiting the hepatic mixed function oxidase enzyme system (68). Cimetidine therapy has been documented to prolong the elimination half-life of several drugs used during anesthesia including diazepam, chlordiazepoxide, theophylline, propranolol, and lidocaine. In the asthmatic patient, administration of cimetidine can block the bronchodilating action mediated by H₂-receptor activation, thereby potentially unmasking the bronchoconstrictive effects produced by H₁-receptor stimulation. Other serious side effects of cimetidine include arrhythmias, hypotension, and CNS depression (which can produce symptoms ranging from drowsiness to coma). Ranitidine, a newer H₂-receptor antagonist, is more potent, more specific, and longer-acting than cimetidine (69). Ranitidine, 100–200 mg orally, is as effective as cimetidine, 200–400 mg orally, in decreasing the number of patients considered to be at risk for aspiration pneumonitis without the side effects and adverse drug interactions associated with cimetidine (70,71).

Why should anesthesiologists concern themselves with drugs used to inhibit gastric acid secretion dur-

Table 4. Common Side Effects after Intramuscular Preoperative Medication[a]

	Percentage of patients				
Product	Dry mouth	Slurred speech	Headache	Dizziness	Nausea
Placebo	34	21	9	7	12
Pentobarbital (50–150 mg)	29	27	10	10	7
Secobarbital (50–150 mg)	40	32	8	8	8
Diazepam (5–15 mg)	35	20	7	10	3
Hydroxyzine (50–150 mg)	45	31	7	6	2
Morphine (5–10 mg)	80	33	12	15	6
Meperidine (50–100 mg)	85	45	3	20	11

[a]From Forrest et al. (7).

ing the preoperative period? Studies indicate that anywhere from 40 to 80% of patients having elective surgery have a gastric pH <2.5 and/or a gastric fluid volume >25 ml at the time of intubation and therefore might be considered at risk for developing acid aspiration (Mendelson's) syndrome (72). Thus a case can be made in favor of prophylactically altering both gastric acidity and volume in an effort to decrease the incidence of aspiration pneumonia (73). What prophylactic agent should be used? Most studies have supported the efficacy of antacids in neutralizing stomach acid. Unfortunately, colloid antacid suspensions can produce serious pulmonary sequelae if aspirated (74), and the only widely studied nonsuspension antacid, sodium citrate, may be less effective in neutralizing gastric acid (75). Preoperative administration of sodium citrate will increase gastric fluid to a pH greater than 2.5 in 68–84% of patients (76); however, it also increases gastric fluid volume (77,78). Metoclopramide, a potent gastrokinetic agent, has proved unreliable in decreasing the residual gastric volume after sodium citrate administration (79). In a comparative study involving sodium citrate and cimetidine, the H_2-receptor antagonist was found to be significantly more effective in decreasing the risk of aspiration pneumonitis (78).

Where do the H_2-receptor antagonists fit into the clinical picture? These compounds can be extremely useful in the perioperative setting (e.g., obstetrical anesthesia). Early clinical studies have not shown any significant effects of these drugs on the fetus when administered to parturients (80). Hodgkinson et al. reported on the results of a multicenter study where parturients undergoing elective cesarean section under general anesthesia were treated with either an antacid (Mylanta I, 30 ml orally, 1–3 hr before surgery) or cimetidine (300 mg orally at bedtime and 300 mg IM, 1–3 hr before surgery) (80). Gastric pH was higher and gastric volume was less in cimetidine-treated patients. Although cimetidine does cross the placental

barrier, the neonatal neurobehavioral scores were similar in both groups. Thus cimetidine (or ranitidine) can be used as a replacement for oral antacids before elective cesarean section. Furthermore, metoclopramide, 10 mg IV, can significantly improve gastric emptying in those parturients requiring either an elective or emergency cesarean section (81). However, the use of metoclopramide, 10 mg IV, in combination with oral antacids appears to be less effective than when the H_2-receptor antagonists are used alone (75). Preoperative administration of oral cimetidine, 300 mg, or ranitidine, 150 mg, in combination with metoclopramide, 10 mg, appears to minimize the risk of aspiration pneumonitis in an elective surgery population (82,83). Recently, O'Sullivan et al. demonstrated that the combined use of metoclopramide and ranitidine may be the most effective pharmacologic approach to decreasing the risk factors for acid aspiration syndrome (84).

Use of Premedication in Outpatients

It is frequently stated that premedication should be minimized or avoided in outpatients because it prolongs the recovery period. Data available in the anesthesia literature do not support this hypothesis. Recent studies indicate that premedication with a short-acting opioid analgesic (e.g., fentanyl, 1–2 μg/kg IV) might decrease recovery time as a result of the analgesic's ability to decrease the anesthetic requirement (85,86). Clarke and Hurtig (87) reported that intramuscular premedication with meperidine, 1 mg/kg, and atropine, 0.01 mg/kg, did not prolong recovery to "street fitness" after outpatient surgery. In a retrospective study, Meridy reported that preoperative administration of diazepam or hydroxyzine did not appear to significantly prolong recovery (88). In pediatric outpatients, oral diazepam, 0.1 mg/kg, or hydroxyzine, 0.5 mg/kg, produced only minimal decreases in anxiety but did not delay emergence or

discharge (89). More recently, oral premedication with a combination of diazepam, 0.2 mg/kg, meperidine, 1.5 mg/kg, and atropine, 0.02 mg/kg, was shown to decrease perianesthetic problems without prolonging recovery in pediatric outpatients (90). In a placebo-controlled, double-blind study involving adult outpatients, Jakobsen et al. reported that oral diazepam, 0.25 mg/kg, significantly decreased preoperative discomfort and apprehension without prolonging recovery (91). Nevertheless, diazepam premedication may impair coordinative and reactive skills for 5–10 hr (92).

Are prophylactic antiemetics useful in the outpatient setting? Nausea and vomiting are common problems in outpatient anesthesia. Etiologies include the patient's medical condition (e.g., pregnancy), assisted ventilation (e.g., air in the gastrointestinal tract), and drugs (e.g., fentanyl, etomidate, isoflurane, nitrous oxide). Some studies indicate that droperidol, 0.5–1.5 mg IV, is an effective antiemetic (93,94); however, the routine use of droperidol may prolong the awakening and recovery times for some patients as a result of its sedative effects (95). Nevertheless, droperidol is useful for outpatients undergoing operations associated with a high incidence of postoperative nausea and vomiting (e.g., strabismus surgery (96), laparoscopy, therapeutic abortions). Alternatively, metoclopramide is an effective antiemetic either orally or intramuscularly at doses that do not appear to prolong recovery from anesthesia (97–99). Metoclopramide appears to be more effective when given prior to the patient's arrival in the operating room (33,95,100). A metoclopramide-cimetidine combination may be useful for decreasing gastric volume, increasing gastric pH, and decreasing the incidence of postoperative nausea and vomiting in selected outpatients (101). Although promethazine and hydroxyzine possess antiemetic activity, both are associated with significant discomfort after intramuscular injection (102). Other clinically effective antiemetics in the outpatient setting include the following: prochlorperazine, 5–10 mg; perphenazine, 1–3 mg; benzquinamide, 25–50 mg; promazine, 5–15 mg; and trimethobenzamide, 100–200 mg.

In conclusion, studies involving patients undergoing ambulatory anesthesia indicate that judicious use of sedative, analgesic, and antiemetic premedicants may be helpful in relieving anxiety, decreasing the anesthetic requirement, and preventing postoperative nausea and vomiting without prolonging recovery.

Use of Drug Combinations

What drug combinations are commonly employed in the preoperative setting? Some of the more popular combinations include sedative-narcotic (52), tranquil-izer-narcotic (50), and anticholinergic-narcotic (48). As mentioned earlier, the combination of morphine and hydroxyzine produced more sedation and analgesia than either drug alone (52). Similarly, promethazine significantly improved anxiolysis, sedation, and patient acceptance when combined with morphine (50). Whereas a combination of premedicants possessing mutually complementary properties may be advantageous, the possibility of adverse drug interactions, and thereby the potential for untoward side effects is frequently increased. Furthermore, drugs from the same pharmacologic groups do not necessarily interact in a similar manner. For example, patient acceptance of morphine is better when it is combined with scopolamine rather than with atropine (48). Scopolamine also significantly enhances the anxiolytic, sedative, and amnesic effects of diazepam (103). Although the advantages of combining diazepam and scopolamine have been demonstrated, the combination of lorazepam and scopolamine produced an unacceptably high incidence of postoperative side effects, including dizziness, confusion, and agitation (104).

Side Effects of Commonly Used Premedicants

What are the relative incidences of side effects associated with commonly prescribed premedicants? Forrest et al. evaluated six widely used premedicants in a randomized double-blind manner after intramuscular administration (7). The study drugs included two barbiturates (pentobarbital, secobarbital), two narcotics (morphine, meperidine), diazepam, and hydroxyzine. Dry mouth, slurred speech, and dizziness were the most commonly reported side effects (Table 4). Nausea occurred significantly less frequently after diazepam and hydroxyzine.

Traditionally, premedication refers to the drugs administered to a patient awaiting an operative procedure. However, the preoperative preparation of a patient for anesthesia and surgery includes both psychologic and pharmacologic components. The psychologic aspect of preoperative preparation is provided by the anesthesiologist's visit and interview. In addition, a wide spectrum of pharmacologic agents (e.g., barbiturates, benzodiazepines, major tranquilizers, opioid (narcotic) analgesics, anticholinergics, histamine H_2-blockers, gastrokinetic drugs) are administered to facilitate the process of preoperative preparation.

Recommendations regarding routine preoperative medication for adults include a preoperative visit and patient interview, an oral hypnotic the evening before surgery (e.g., flurazepam, triazolam), and an oral sed-

ative-anxiolytic 60–90 min before surgery (e.g., diazepam). Midazolam may be the sedative-anxiolytic of choice for intramuscular administration. If analgesia is needed, one can order an opioid analgesic (e.g., morphine, meperidine) or substitute a sedative-narcotic or anticholinergic-narcotic combination. If prolonged amnesia and sedation is desired (105), lorazepam would be a useful sedative-anxiolytic. Preoperative administration of aqueous antacids (sodium citrate, Alka-Seltzer®) will effectively increase gastric pH in patients undergoing emergency surgery (106). For elective surgery patients at risk for aspiration pneumonitis, cimetidine or ranitidine alone, or in combination with metoclopramide, is recommended. The H_2-receptor antagonists may also be useful in combination with a H_1-receptor antagonist (diphenhydramine) in the preoperative preparation of the allergy prone patient (107). Glycopyrrolate is a highly effective antisialagogue, whereas atropine would be the vagolytic drug of choice (108). If an antiemetic is desired (e.g., patients with a history of nausea and vomiting after general anesthesia), droperidol, metoclopramide or both are useful. Finally, if additional sedation or anxiolysis is required at the time the patient enters the operating room, titrated intravenous doses of diazepam or midazolam can be used to rapidly achieve the desired degree of sedation and amnesia (109,110). The parenteral administration of a benzodiazepine prior to induction of anesthesia would be expected to decrease the anesthetic requirement (Table 3) (111,112).

In conclusion, most anesthesiologists would agree that relief of anxiety is an important objective of preoperative preparation. Both psychologic support and pharmacologic agents are useful in minimizing anxiety during the preoperative period. Other goals of premedication include sedation; analgesia; amnesia; antiemetic and antisialagogue actions; increased gastric fluid pH (>2.5) and decreased gastric fluid volume (<20 ml); and prophylaxis against allergic reactions. The drug choice and dosage will depend on the patient's age, weight, ASA physical status, current medications, and history of adverse drug reactions, as well as the type and duration of the surgical procedure. The timing and route of drug administration may be as important as the drugs actually chosen for premedication. If the premedicant is properly selected and administered in an appropriate fashion, it can produce the desired pharmacologic actions without adverse side effects or drug interactions. Contrary to popular opinion, most commonly used premedicants do not significantly delay recovery after anesthesia. Even though benzodiazepines and narcotic analgesics produce dose-dependent central nervous system depression, these agents do not necessarily prolong

the recovery period because of their ability to decrease the patient's anesthetic requirement (41–43,111–112). Thus, the rational use of premedication can make the experience of surgery safer and more pleasant for our patients without increasing health care costs. By limiting one's practice to one or two drugs in each of the various premedicant drug groups, the practicing anesthesiologist will become more familiar with the effects of these drugs and be better prepared to alter their "premedication routine" to meet the specific needs of the individual patient.

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Clinical Reports

Junctional Rhythm in a Patient with Mitral Valve Prolapse

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Mitral valve prolapse is considered the most common cardiac valvular abnormality. It has been associated with various electrocardiographic changes and dysrhythmias in the perioperative period, including ST–T wave changes, T-wave inversions, ventricular premature depolarization, and supraventricular tachycardia (1–6). We present the first case in the world literature of junctional rhythm after general anesthesia in a patient with previously undiagnosed mitral valve prolapse.

Case Report

A 29-yr-old woman was scheduled for a dilation and uterine curettage, colposcopy, and cone biopsy of the cervix. There was no past history of cardiovascular disease. Prior surgical history included an uneventful tonsillectomy as a child under general anesthesia. Preoperative examination revealed a healthy woman with a blood pressure of 110/80 mm Hg and a regular pulse rate of 84 beats/min. Her chest and cardiac examination was normal without audible cardiac murmurs or clicks. Laboratory examination revealed normal electrolytes and hematocrit. Chest x-ray was also normal. The electrocardiogram (ECG) showed a normal sinus rhythm. Premedication consisted of morphine sulfate, 10 mg, and promethazine, 50 mg, intramuscularly (IM) 1 hr prior to arrival in the operating room. Anesthesia was induced with thiamylal sodium, 300 mg, and was maintained with droperidol, 0.625 mg, 65% nitrous oxide, and 1–1.5% enflurane in oxygen, with spontaneous respirations. The end-tidal CO_2 concentration measured by mass spectrometry ranged from 40 to 47 mm Hg throughout anesthesia. Vital

signs were stable throughout the 30-min procedure with a regular sinus rhythm on the ECG monitor. After emergence from anesthesia, the patient was transferred in stable condition to the recovery room where a junctional rhythm at 65 beats/min alternating with a sinus rhythm at 75 beats/min was noted on the ECG monitor (Fig. 1). A 12-lead ECG showed a junctional rhythm at a rate of 58 beats/min alternating with a sinus rhythm with no other changes from the preoperative ECG. The patient was awake and alert with adequate spontaneous ventilation on 35% O_2 by mask and had a stable blood pressure at 120/70 mm Hg. An arterial blood sample showed the pH to be 7.37, the P_{CO_2} 40 mm Hg, the P_{O_2} 94 mm Hg, and calculated HCO_3^- 23.4 mEq/L. Serum electrolyte levels, including sodium and potassium, were normal. The junctional rhythm persisted for 2 hr in the recovery room and then spontaneously converted to normal sinus rhythm. Physical examination including hand grip, the Valsalva maneuver, and changes in position failed to elicit a cardiac click or murmur. A two-dimensional and M-Mode echocardiogram performed later that day (postoperatively) revealed mitral valve prolapse of the anterior mitral leaflet (Fig. 2). Serial ECGs revealed no changes from the preoperative tracing. The patient was discharged on the first postoperative day in stable condition.

Discussion

Mitral valve prolapse was first described in 1958 by Fernex and Fernex (7) and demonstrated by angiography by Barlow et al. (8) in 1963. The incidence of mitral valve prolapse has been reported to range from 0.5% to 17% in healthy individuals (2,9). It is most common in females from 30 to 50 yr of age. As the population ages, the differences between sexes decreases. Mitral valve prolapse may be acquired or more commonly inherited as an autosomal dominant inheritance (10).

SINUS RHYTHM

JUNCTIONAL RHYTHM

Lead V1

Lead II

Lead V6
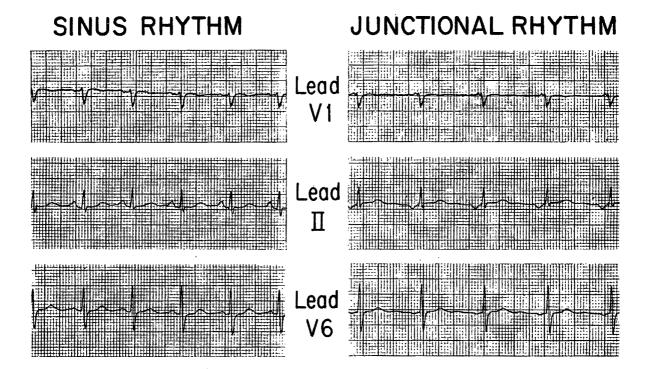
Figure 1. Left side: sinus rhythm before and after dysrhythmia. Right side: junctional rhythm at 75 beats/min in the recovery room.
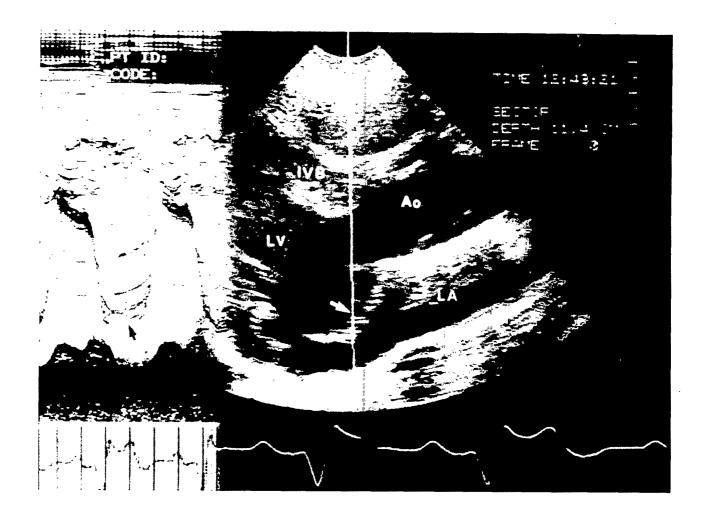
Although the majority of patients with mitral valve prolapse are asymptomatic, symptoms including chest pain, palpitations, poor exercise tolerance, or light headedness may be noted. Potentially serious complications of mitral valve prolapse have been reported in 1–13% of cases, including sudden death due to ventricular fibrillation, bradyarrhythmias, acute chordae rupture, coronary spasm, and bacterial endocarditis (11,12). Central nervous system effects due to emboli originating from the mitral valve such as transient ischemic attacks and partial nonprogressive strokes have been reported (2).

Diagnostic criteria in mitral valve prolapse include a mid or late systolic click accentuated by the Valsalva maneuver, standing, squatting, left lateral decubitus position, or inhalation of amyl nitrate, all which decrease left ventricular volume. The click is thought to be due to deceleration of blood within the undersurface of the prolapsing valve. A late or holosystolic murmur may also be heard. This is thought to be due to mitral regurgitation secondary to redundancy of the leaflets, particularly the posterior leaflet, which leads to inability of the valve leaflets to oppose each other. A reduction in the ventricular volume allows the cavity to become smaller, and the valve prolapses earlier. Increases in sympathetic activity or decreases in peripheral vascular resistance increase cardiac

emptying and also result in early prolapse of the valve. The excessive traction on the chordae tendinae and papillary muscles of the prolapsing leaflets may cause myocardial ischemia and ensuing dysrhythmias (13).

Electrocardiographic abnormalities occur in two thirds of patients with mitral valve prolapse. About one third have T-wave inversions or flattened T waves in Leads II, III, AVF, with or without ST–T wave changes. A variety of dysrhythmias have been reported (14): premature ventricular depolarizations (11,15–17), sinus bradycardia (18), various supraventricular dysrhythmias, Wolff-Parkinson-White syndrome (19,20), AV conduction block, and left and right bundle branch block (21). Therapy for symptomatic patients includes propranolol, which decreases heart rate and increases left ventricular volume, reducing the degree of prolapse and stretching of the mitral valve leaflets. Rare cases of hemodynamically significant bradycardia have required cardiac pacing (19). For most patients, the dysrhythmias are benign and do not require treatment. Diagnosis is confirmed by echocardiography. Once the diagnosis is established, prophylactic antibiotics are currently recommended by the American Heart Association for dental, gastrointestinal, or genitourinary procedures for the prevention of bacterial endocarditis (13).

No report exists in the literature regarding a junctional dysrhythmia associated with mitral valve prolapse, as was the case with our patient. Because the junctional rhythm persisted for 2 hr after anesthesia was terminated, it would be difficult to explain the

Figure 2. Left side: M-mode echocardiogram of mitral valve. Arrow points to holosystolic "prolapsing" consistent with the diagnosis of mitral valve prolapse. Right side: Parasternal long axis two-dimensional echocardiogram demonstrating hammocking of the mitral valve (arrow) into the left atrium (Ao, Aorta; IVS, interventricular septum; LA, left atrium; LV, left ventricle).

dysrhythmia on the basis of hypercarbia, hypoxia, electrolyte imbalance, light anesthesia, or arrhythmogenicity of the inhaled anesthetic, enflurane. The dysrhythmia may be explained on the basis of increased sensitivity to catecholamines reportedly seen in patients with mitral valve prolapse (22) coupled with the high catecholamine levels reported in patients throughout the perioperative period. Although droperidol, an α-blocker with a duration of action up to 6–8 hr, was given, it is unlikely that the dosage used during the case was sufficient to cause a reduction in ventricular volume precipitating the prolapse and the dysrhythmia.

The pathophysiology of mitral valve prolapse should be borne in mind when administering an anesthetic, although most patients with mitral valve prolapse usually have no hemodynamic consequences. Factors that reduce end-diastolic volume, decrease preload or afterload, or increase myocardial contractility or heart rate have been shown to increase the redundance of the leaflets, resulting in prolapse and increasing the incidence of dysrhythmias.

In general, the following measures should be taken in patients with mitral valve prolapse: Premedicate appropriately to reduce catecholamine release. By maintaining adequate depth of anesthesia and minimizing catecholamine release, factors that increase dysrhythmias such as hypercarbia, hypoxia, hypo- or hyperkalemia may be avoided. Drugs that increase heart rate, such as atropine or pancuronium, or anesthetics that increase blood pressure, such as ketamine, should be avoided if possible. Avoid use of vasodilators; avoid extreme head-up or sitting positions; blood volume should be maintained; reduce the effect of positive pressure ventilation on cardiac output by infusing adequate fluids; and avoid widespread vasodilatation with spinal-epidural anesthesia.

When a dysrhythmia occurs in the perioperative period the usual measures should be undertaken to

rule out the other common etiologies before it is assumed that mitral valve prolapse is the cause. It is proposed that mitral valve prolapse may be the culprit in many newly occurring dysrhythmias. Most patients, however, with mitral valve prolapse usually have an uneventful anesthetic. The dysrhythmias either resolve spontaneously or after standard antiarrhythmic therapy, and usually do not require evaluation or treatment.

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Generalized Grand Mal Seizure after Recovery from Uncomplicated Fentanyl–Etomidate Anesthesia

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There have been a number of reports of seizure-like activity after fentanyl administration (1–4). These have been associated with a variety of doses of this opioid (100–2500 μg) and have ranged from focal clonic movements (4) to typical generalized grand mal seizures (2,3). In all these reports the seizures occurred either during or very soon after the administration of the drug (2,3). We report the occurrence of a typical tonic and clonic grand mal seizure in an apparently fully recovered, conscious patient after uncomplicated fentanyl, etomidate, and oxygen anesthesia given for a short surgical procedure.

Case Report

A 45-yr-old woman weighing 59 kg was admitted for cystoscopy and dilation and curettage on an ambulatory basis. She presented with no relevant previous medical history and no family history of medical disorders, including epilepsy. She had no known allergies and had been taking no medications for 12 months before operation. Prior to this she had had one course of ampicillin for a throat infection in the past 10 yr. Clinical examination was normal, and our unit's standard laboratory tests for day surgery patients (hemoglobin and urine analysis) were unremarkable. Premedication of papaveretum, 10 mg, and scopolamine, 0.2 mg was given intramuscularly 1 hr preoperatively. Before induction of anesthesia arterial blood pressure was 120/80 mm Hg, heart rate 80 beats/min, and the ECG demonstrated sinus rhythm.

General anesthesia was induced through an indwelling needle. Fentanyl, 150 μg, was first administered followed by etomidate, 20 mg, with repeated

doses given during the procedure as we have previously described (5). A total dose of 35 mg of etomidate was administered, and the patient was given oxygen, 8 L/min, via a Bain type coaxial breathing system. Blood pressure, heart rate, and ECG remained stable throughout the procedure, and the respiratory rate was stable at 12–14 breaths/min. Anesthesia was terminated after 10 min, and the patient was transferred to the recovery room. •

The patient became fully orientated 1.5 min after the termination of anesthesia. She was able to give the correct date and knew her name as well as where she was. Blood pressure, heart rate, and respiration remained stable during this time. Two minutes after regaining consciousness the patient suddenly developed severe and generalized clonic convulsive movements of the body with bilateral dilation of the pupils. Her arterial blood pressure increased to 150/70 mm Hg, the heart rate increased to 120 beats/min, and she became unconscious. There was no loss of bowel or bladder control. Diazepam, 10 mg, was administered intravenously, and this successfully terminated the convulsion. The duration of the seizure was approximately 90 sec, and the patient regained consciousness 2 min after the injection of diazepam. She had total amnesia for the event. Subsequent neurologic examination revealed no abnormality. An electroencephalographic examination performed approximately 7 hr after the seizure was normal. The patient left hospital the following day with no recollection of the event. On three consecutive visits in nine months clinical examination was negative.

Discussion

The anesthetic most widely recognized as having epileptogenic properties is the inhalation agent enflurane. Enflurane increases cortical activity and may cause grand mal seizures, even 2–3 days after its administration (6). Intravenous induction agents and anal-

gesics in clinical doses have not been commonly associated with grand mal seizures.

Since its introduction into clinical practice, etomidate has been reported to cause involuntary myoclonic movements during the induction and maintenance of anesthesia (7,8,9). Although these involuntary movements may resemble a cerebral seizure, there is no evidence that they are epileptiform in nature (7). Indeed, etomidate is known to possess potent anticonvulsant properties. These have been demonstrated in animal studies (10,11), and in humans etomidate has been used to terminate therapy resistant status epilepticus (12,13). Although myoclonic movements may be reduced by the preinduction administration of fentanyl (5), this is not as successful as it is with methohexital (14). Postoperative myoclonic movements have been less well documented, although some reports have been published (7,9), including one reporting prolonged movements of a few hours' duration (7).

It is well documented that fentanyl may cause muscular rigidity during both induction and maintenance of anesthesia (15), as well as in the postoperative period (16), the later probably being due to the occurrence of a secondary plasma peak (17). In addition, large doses of all narcotics have the potential to produce central nervous system excitation (18), but the dose of fentanyl that produces true seizure activity in humans is not known (4). However, Carlsson et al. have reported seizure-like activity in animals (rats) during the administration of high doses of fentanyl (200–400 μg/kg) (19). Also, in humans the infusion of fentanyl has been reported as being associated with isolated sharp wave activity on the EEG (20). This occurred about 2 min after the start of the infusion and was more evident with increasing doses of fentanyl, occurring in some 80% of patients at 70 μg/kg. Rao et al. have reported grand mal type convulsions after the rapid intravenous administration of fentanyl (2250 μg and 2500 μg) (1). Although their report has been challenged by Sebel and Bovill (who suggested that unmodified muscle rigidity was the most likely explanation) (21) Rao and El-Etr have little doubt that true seizures had occurred in their patients (22).

There are two more reports of grand mal type seizures after the administration of small doses of fentanyl (1–2 μg/kg) (2,3). Scott and Sarnquist (4) have also reported seizure-like activity but without characteristic EEG changes during fentanyl infusion (4). Scott and Sarnquist suggested (as had Sebel and Bovill) (20) that this, and other reported cases, may not have been true cortical seizures but rather myoclonic movements of a severe type (14,20).

Thus there are a number of possible explanations

for the sequence of events we have reported: either an exaggerated manifestation of muscle rigidity or myoclonic movements caused by etomidate or fentanyl (a peripheral manifestation) or a true epileptiform seizure caused by either agent (a central effect). In our case, after uneventful anesthesia using fentanyl and etomidate, generalized clonic convulsions occurred after an initial tonic phase. The convulsions were undoubtedly "grand mal" in nature, were witnessed by several experienced clinicians, and responded promptly to anticonvulsant therapy with diazepam. We thus believe that a true central epileptiform seizure had taken place, a belief supported by the timing of events in which the seizure occurred after full recovery from anesthesia.

Etomidate possesses not only cerebral protective properties (23), but also potent anticonvulsant properties (10–13). It therefore seems most likely that the seizure was due to the administration of fentanyl, and it is possible that the fit occurred when the anticonvulsant properties of etomidate were waning with reduced cerebral levels after recovery. We suggest our report adds to the available evidence that fentanyl, even in low doses, may occasionally precipitate a true epileptiform seizure.

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Anesthetic Implications of Protein C Deficiency

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Protein C is an essential, circulating, vitamin K-dependent anticoagulant synthesized in the liver. It inhibits the activated clotting factors V and VIII and stimulates fibrinolysis (1–4). Acquired protein C deficiency may occur in patients with hepatic disease, disseminated intravascular coagulation, adult respiratory distress syndrome, and in patients after surgery (1,5,6). Inherited deficiencies are transmitted in an autosomal codominant fashion and, although rare, increasingly are being recognized (7–9). Mild protein C deficiency, either acquired or inherited heterozygously, usually presents in adults. Such deficiencies may be associated with a tendency for thrombophlebitis, usually superficial, although deep venous thrombosis and pulmonary embolism also occur (2,9,10). In addition, thrombotic renal involvement and central nervous system and myocardial infarction may occur (8,11). Congenital, homozygous protein C deficiency presents in infancy and is usually severe. Purpura fulminans, massive cutaneous necrosis, gangrene, and widespread venous thrombosis, which is frequently fatal, have been reported (12,13). Thrombosis may be triggered by endothelial damage, immobility, and blood stasis, all of which may occur during anesthesia.

We were consulted about anesthesia for an infant with congenital protein C deficiency about whom serious concerns were raised regarding the anesthetic management, including the safety of tracheal intubation. Because we were unable to find any reports concerning the anesthetic management of these patients, we now report our experience and discuss the anesthetic implications of protein C deficiency.

Case Report

A 3.5-month-old infant presented for partial omentectomy and placement of a Tenkoff peritoneal dialysis catheter. By the first day of life he had skin necrosis over pressure points and bilateral retinal hemorrhages. Diagnostic studies revealed protein C antigens ranging from 11–19%, with activities consistently less than 6% of normal (14). Simultaneously obtained factor X antigens were normal for age. Both parents had protein C antigens and activities in the range expected for heterozygotes. These findings suggest a homozygous abnormality of protein C in the infant. One week prior to surgery, he developed progressive renal failure and hypertension. Therapy included exchange transfusion, fresh frozen plasma, sodium nitroprusside, diazoxide, hydralazine, and furosemide. Despite therapy, progressive renal failure, hypertension, and congestive cardiac failure necessitated dialysis. The decision was made to place a Tenkoff peritoneal catheter. At the time of surgery, the heart rate was 170 beats/min, systolic blood pressure 150 torr, respiratory rate 62/min; the abdomen was distended, lungs were clear, and he had an S_3 gallop rhythm. Blood urea nitrogen was 100 mg/dl, creatinine was 6.5 mg/dl, and hematocrit was 18%.

Various anesthetic plans including local, regional, and general anesthesia were considered. Particular concern about airway and tracheal trauma was expressed, as submucosal thrombosis and necrosis were considered a potentially serious threat. After a routine infusion of 10 ml/kg fresh frozen plasma to replace protein C, anesthesia was induced by rapid sequence with thiopental followed by succinylcholine. The patient's trachea was intubated with a 3.0-mm oral tube. There was an air leak at a pressure of 5 cm H_2O. After 1.5 hr of uneventful surgery with nitrous oxide, oxygen, halothane, and pancuronium, the neuromuscular blockade was reversed (neostigmine, 0.3 mg, and atropine, 0.2 mg) and the patient was extubated awake. In the postoperative period, the patient remained afebrile, without stridor, with clear breath

sounds, and the chest x-ray remained normal. Five days later, revision of the Tenkoff catheter was required. We felt that before repeating tracheal intubation, bronchoscopic examination of the airway was indicated to determine whether untoward sequelae had occurred after the previous intubation. After a smooth inhalation induction with nitrous oxide, oxygen, and halothane, the airway was examined using a 3.5 mm Machida flexible laryngoscope. The upper airway and trachea were entirely normal. The trachea was again intubated with a 3.0 mm orotracheal tube with, again, an air leak at 5 cm H_2O. The 1.5-hr intraoperative and the postoperative course were again uneventful without evidence of respiratory complications. Five days later the patient's condition improved to such an extent that removal of the Tenkoff catheter was performed under general anesthesia. Repeat bronchoscopic airway examination again revealed no abnormalities, and so a 3.0-mm oral endotracheal tube was once more inserted, again with an air leak at 5 cm H_2O. No postoperative respiratory complications occurred. One hundred twenty days after the final airway manipulation, no respiratory or airway complications were present. The patient continues to require replacement therapy to treat his protein C deficiency.

Discussion

The predilection for disseminated venous thrombosis and its consequences in children suffering from protein C deficiency is well-recognized (2,7–9,11–13). Our patient had already demonstrated severe superficial necrosis over pressure points, and the question was raised whether general anesthesia, immobility, and compromised tracheal blood flow caused by endotracheal intubation might lead to potentially fatal airway complications. For this reason, serious consideration was given to anesthetic plans other than general endotracheal anesthesia. It was felt that local anesthesia would not provide adequate pain relief or optimal operative conditions. Although spinal and caudal epidural anesthesia have been successfully used in neonates and infants (15,16), we felt that crying, coughing, or screaming could cause visceral herniation. In addition, there was potential for local tissue damage and necrosis in the vicinity of the spinal cord that could cause a neurological catastrophe. Ultimately, despite our concerns, we decided that in order to ensure a safe airway, provide optimal operative conditions, and guarantee adequate oxygenation, general endotracheal anesthesia would be the wisest choice.

A rapid sequence intubation was indicated because of the infant's distended abdomen. A small (3.0-mm)

endotracheal tube was selected to decrease the risk of tracheal compression. The presence of a low pressure air leak reassured us that this risk was minimized. The use of an uncuffed tube was felt to be essential and is routine pediatric practice. The risk of aspiration around an uncuffed endotracheal tube has been shown to be unrelated to the size of the leak (17). The absence of fever and respiratory symptoms and a normal chest x-ray after the procedure did not eliminate the possibility of tracheal damage. We therefore decided that, should the necessity for further surgery arise, direct endoscopic inspection of the entire airway would be warranted. On two occasions it was possible to visualize an entirely normal upper and lower airway. In addition, the pressure at which an air leak occurred around a 3.0-mm endotracheal tube did not change, supporting the notion that significant airway swelling had not occurred (18,19). We are reassured by the lack of evidence to support the theoretical contention that significant airway sequelae would follow endotracheal intubation performed in this fashion in a patient with severe, homozygous protein C deficiency.

Therapy directed at correcting the protein C deficiency includes transfusion with fresh frozen plasma on a regular basis, as frequently as every 12 hr, or infusion of factor IX concentrate, which is also rich in protein C (1,2). However, it should be noted that factor IX concentrate therapy may induce thrombosis or disseminated intravascular coagulation (20,21). Complications of replacement therapy are hyperproteinemia and hyperviscosity, for which an exchange transfusion may be indicated prior to anesthesia. Anticoagulants have also been used including heparin and coumarin, with varying success (1,7). Clearly specific protein C replacement would be preferable, but it is, as yet, not available (2,6).

In summary, we present an infant with congenital protein C deficiency who safely underwent three general endotracheal anesthetics without complication. Despite the real concerns of tissue damage, safe endotracheal intubation is possible. Anesthestic management should include preoperative protein C replacement, atraumatic technique, and, we believe, insurance of a sufficient air leak around the endotracheal tube. It may also be appropriate to consider alternatives to general anesthesia if surgical needs allow.

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Perioperative Management of a 430-Kilogram (946-Pound) Patient with Pickwickian Syndrome

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The patient with massive morbid obesity and Pickwickian syndrome poses a number of unique problems for the anesthesiologist. We present the case of a 430-kg patient who required aggressive preoperative therapy and an unusual solution to an intraoperative problem.

Case Report

A 46-year-old male, 170 cm in height, and estimated to weigh 385 kg, presented with increasing dyspnea at rest and a pyogenic panniculitis. He was transferred to this institution for panniculectomy and bilateral mastectomies.

Past history was unremarkable except for extraordinary weight all his life. Physical examination revealed a massively obese, somnolent male lying on his side. When supine he complained of severe dyspnea. Breath and heart sounds were inaudible. An ulcer with a surrounding area of cellulitis was present in one of the many folds of his massive panniculus.

His hematocrit was 55%, SGOT 660 U, SGPT 1700 U, LDH 522 U, prothrombin time 18 sec (control 12 sec). Arterial blood gas tension while breathing room air supplemented with 2 LPM oxygen via nasal cannulae included a pH of 7.32, Pao_2 of 44 mm Hg, and a $Paco_2$ of 67 mm Hg. The electrocardiogram showed an anterior wall myocardial infarction of indeterminate age. A chest radiograph was technically unsatisfactory.

Increasing the inspired oxygen concentration through the use of a ventimask resulted in a pH of 7.27, a Pao_2 of 47 mm Hg, and a $Paco_2$ of 94 mm Hg. Therefore, the patient was then intubated nasally with

an 8-mm endotracheal tube and mechanically ventilated at a rate of 12 breaths/min using a tidal volume of 900 ml with continuous positive airway pressure of 5 cm H_2O and an inspired oxygen concentration of 35%. Subsequent arterial blood gas tensions revealed the pH to be 7.35, the Pao_2 73 mm Hg, and the Pco_2 66 mm Hg. He was fed through a nasogastric tube and was treated with vigorous pulmonary toilet, bronchodilators, and antibiotics for the next 10 days. At this time his arterial blood gases were stable, and prothrombin time and liver function tests had returned to normal. However, the patient still could not tolerate the supine position. A bed was therefore constructed for the patient to allow him to be transported to the operating room, and also for him to be operated upon and nursed in.

On the 14th hospital day he was taken to the operating room for panniculectomy. He arrived in the lateral position with the endotracheal tube in place and was given 25 mg of diazepam and placed on controlled ventilation. Two large bore intravenous cannulas were placed percutaneously, and a radial artery cannula was inserted via cutdown. A pulmonary artery catheter could not be passed via the internal jugular or anticubital routes. The patient remained in the lateral position during this time. The surgical plan was to pass a sterile stainless steel rod transversely through the panniculus and then to suspend the panniculus through the use of an automotive engine crane while the panniculectomy was performed. This required the patient to be in the supine position, and there was concern as to whether he could be ventilated in this position. Therefore an epidural anesthetic was performed at approximately L3–4 through an 18-gauge disposable Hustead needle with the aid of an assistant applying pressure to the back in the area of the interspace. After a test dose, 18 ml of 3% chloroprocaine was administered and a catheter placed. Satisfactory anesthesia was obtained, and the rod was inserted under aseptic conditions. The rod was then attached to the crane with cables, the pan-

niculus suspended, and the patient turned supine. Once it was ascertained that the patient could be ventilated, fentanyl, 300 μg, diazepam, 10 mg, 50% nitrous oxide, and 0.5% isoflurane were administered. Thirty minutes after the initial dose, 20 ml of chloroprocaine was administered, and 60 min later an additional 20 ml of 0.5% bupivicaine was given via the epidural catheter.

The patient's condition remained stable throughout the surgical procedure. The arterial blood gases were maintained in the range of Pao_2 100 and $Paco_2$ 50 mm Hg. A 47 kg panniculus was removed. The patient required 10 U of packed red cells, 250 ml of fresh frozen plasma and 9 L of lactated Ringer's solution. The patient was extubated on the third postoperative day. He developed a wound infection, which responded to antibiotics and debridement. Subcutaneous heparinization 12,000 U every 12 hr was instituted on the fifth postoperative day and continued throughout the remainder of his hospitalization. After the first procedure the patient appeared less somnolent and was able to sit on the side of his bed with minimal dyspnea. His major complaints concerned the food.

On the 41st hospital day the patient was taken to the operating room for bilateral mastectomies. After the insertion of three large-bore intravenous cannulas and a radial artery cannula, his nasopharynx was anesthetized with 5% cocaine, and an awake intubation was performed. Anesthesia was maintained with diazepam, 20 mg, fentanyl, 500 μg, nitrous oxide 50% and isoflurane, 0.75%. Breast tissue weighing 7.5 kg was removed. The patient tolerated the procedure well and was extubated on the first postoperative day. His respiratory status continued to improve.

On the 51st hospital day the patient suddenly became restless, severely dyspneic, and suffered a cardiopulmonary arrest from which he could not be resuscitated. At necropsy his weight was 430 kg. He had sustained a massive acute pulmonary embolus and there was evidence of earlier smaller emboli. He had cardiomegaly, right ventricular and septal ischemia, passive congestion of the liver, organomegaly, and infected surgical wounds. Examination of the specimens taken from the panniculus and breasts revealed phlebosclerosis, suggesting that the patient suffered from ongoing thrombosis despite heparinization.

Discussion

The morbidly obese patient presents major cardiopulmonary, metabolic, hepatic, and technical problems to the anesthesiologist during the perioperative period (1–3). Although the Pickwickian syndrome has been well-described, there are few reports describing the perioperative problems associated with this particular subset of patients, especially a patient weighing greater than 400 kg. The patient with the Pickwickian syndrome is one who is massively obese, has episodic somnolence, and hypoventilates. This triad leads to arterial hypoxemia, respiratory acidosis, polycythemia, pulmonary hypertension, and cardiac failure (4,5). Our patient's condition was further complicated by the fact that he had had a previous myocardial infarction. The preoperative cardiopulmonary treatment of these patients is extremely critical to the surgical outcome. The principle treatment of alveolar hypoventilation is to improve alveolar ventilation. The approach must be individualized for each patient. At one end of the spectrum are antibiotics, pulmonary toilet, hydration, and bronchodilators. Oxygen therapy is directed toward restoring arterial saturation to greater than 80%. If oxygen administration in reasonable concentrations further compromises carbon dioxide elimination, then tracheal intubation and ventilation becomes the treatment of choice (4). Our patient was in the latter category, requiring assisted ventilation to reverse his acidosis, hypoxemia, and cardiac failure.

The panniculectomy performed in our patient was carried out in an effort to reduce body weight, allow for easier ambulation, improve hygiene, and reduce intraabdominal pressure when the patient was supine. The concern of ventilating the patient while supine, even with the panniculus suspended, led to the performance of an epidural anesthetic for the initial instrumentation and suspension of the panniculus. Regional anesthesia allowed us to suspend the panniculus and place the patient in the supine position while he was still awake and able to breathe spontaneously. When it was determined that mechanical ventilation was possible he was then anesthetized as described above. The avoidance of muscle relaxants, minimization of narcotics, and the potential for decreased blood loss were additional advantages of using a regional anesthetic in this patient. After the panniculectomy the patient's cardiopulmonary status continued to improve despite a wound infection, a common complication of this procedure (4). The mastectomies were performed in an effort to improve his chest wall compliance. After the latter procedures, his perioperative course was uncomplicated until he developed an acute pulmonary embolus. Examination of the surgical specimens revealed evidence of ongoing peripheral venous thrombosis, which occurred despite low-dose heparinization and physical therapy. More information is needed regarding the dos-

age and efficacy of low-dose heparinization in a patient of this size. The use of a mechanical device such as a vena caval umbrella might also be considered in this high-risk group of patients.

The literature is replete with studies of the morbidly obese. Although Pickwickian patients have been described, there are few reports of this group of patients during the perioperative period. There are none that describe a patient of this size. Preoperative evaluation, treatment, and planning cannot be overemphasized if the surgical outcome is to be successful.

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Letters to the Editor

Selective Remembering:

Anesthesia and Memory

To the Editor:

Eich et al. (1) have written a theoretically important paper distinguishing among awareness, amnesia, and memory in relation to anesthesia. These distinctions are especially important to anesthesiologists because often it has been concluded from verbal recall data that an original perception did or did not take place. For example, "I never dream at night" is a statement about lack of recall of dreaming rather than lack of dreaming, i.e., all people have REM periods and will report dream mentation if awakened during these periods.

The authors are to be commended for dispelling this common misconception in favor of a more sophisticated approach based on laboratory and clinical data. That approach, which the authors spell out, argues that the amnesia observed in ordinary queries of postsurgical patients is insufficient as a guarantee that memories inaccessible to verbal systems may not have formed during the period in question. Specifically, Eich et al. argue that over the past 20 years, other research, including our own (2), has framed a position that personally meaningful statements made to anesthetized patients may affect them whereas personally neutral information is less likely to show influences (3). The mechanisms for understanding these findings are probably similar to the phenomena described some 30 years ago by Colin Cherry (4) as "the cocktail party phenomenon" and responsible for the fact that "preattentive processes" often call our attention to important auditory events, e.g., while fully engaged in one conversation my attention is suddenly drawn to someone mentioning my name in another conversation.

Additionally, the authors point out that the methods of assessing the effects of material presented during anesthesia are unlikely to be revealed through verbal tasks, though at least one study using very sensitive signal-detection analyses did show effects from verbal dependent measures from material presented during deep inhalational anesthesia (5).

However, despite a theoretically intelligent approach, there are problems with the Eich, Reeves, and Katz paper.

Problems with the experiment: The first problem is the selection of the task as presented to both control and experimental groups. There are three major issues: 1) The importance of the task to the patients: Though stating that pertinence is an important independent variable, Eich et al. presented the list of meaningless words at a critical time in the patient's surgery—surgical incision. Though referring to a 1977 review article on the topic (3), the authors chose to ignore the recommendation of pertinence of the material presented to patients under anesthesia. 2) The reliance upon verbal recall as an indicator of having perceived and been altered by the information: Though arguing that tests of verbal retention are insensitive measures of learning during anesthesia, the material presented to patients was repetitive presentations of word pairs out of any context and without meaning. The dependent measures, recognition memory and spelling bias, all rely upon verbal retrieval processes. Additionally the fact that control groups did recognize and spell the words in the intended direction means only that patients were aware of the experimenters' demands, since they were not amnesic in any way, as were the subjects in the original studies forming the basis for the present effort. Since it is apparent from questioning postsurgical patients that verbal retrieval processes are severely depressed, designing a task that depends entirely upon verbal retrieval seems unlikely to succeed. 3) The failure to state the levels of anesthetic agents, premedications, and intravenous drugs: Of interest to research examining perception during anesthesia are the positive findings reported by the authors in the paper. Specifically, two of 48 patients had "accurate retrospective reports of actual intraoperative events" (p 1146) though the levels of agents administered to these patients is not provided. What were the agents and the amounts administered? We do not know. These positive findings are then dismissed without discussion of mechanisms or theories of registration or retrieval of events under general anesthesia.

The task as presented to patients is not pertinent and it relies on verbal retrieval processes, albeit indirect ones. By the authors own theoretical argument, their empirical task would not be expected to be successful.

Problems with the argument: The authors have made logical errors in basing a conclusion upon a negative result, i.e., attempting to prove the null hypothesis. The statement at the end of the article, "At present, however, the conclusion appears compelling that intraoperative events cannot be postoperatively remembered—either with or without awareness," is scientifically unfounded because the same paragraph references studies which have in fact shown these "remembrances without awareness" from information presented during anesthesia. The cases of accurate intraoperative memory reported in their own article are similarly "forgotten." More important, though, is the fact that if one study does not give evidence of a phenomenon, this does not lead to the conclusion that the phenomenon does not exist! It is as if there are two philosophically opposed viewpoints within the same article: one explaining the evidence for a clinically important issue in anesthesia and the other wishing it were not so. Hopefully serious attempts will be made towards developing a model and a theory to explain animal and human data on learning and memory during states of surgical anesthesia. Such attempts must incorporate data from fields as diverse as endocrinology, cognitive psychology, anesthesiology, and neurophysiology.

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Epidural Ketamine for Control of Postoperative Pain: Two Comments

To the Editor:

We read with interest the report by Islas et al. describing postoperative pain control using epidurally administered ketamine (1). The patients in their study had lower abdominal, perineal, or lower extremity elective surgical procedures performed under epidurally administered lidocaine or bupivacaine anesthesia. All patients had postoperative analgesia without respiratory depression. Ketamine was given as a single bolus injection of 4 mg and was judged to provide pain relief in excess of 4 hours in 60% of the patients.

In our experience, from unpublished results of a 1982 study approved by the Hospital Human Investigation Com-

mittee, epidurally administered ketamine (7 mg) followed by a continuous infusion of 10 mg/hr provided significantly less postoperative pain relief than morphine, bupivacaine, or bupivacaine and morphine, the latter combination being considered excellent (2,3). Seven of nine patients (six total hip replacements, two thoracotomies, one laparotomy) required one or more supplemental intramuscular doses of either 6–8 mg of morphine or 50–75 mg of meperidine to attain adequate pain relief. The epidural injections were judged to be adequate in only two individuals, and one of these patients also had urinary retention. Additionally, two patients with chronic back pain received a single, 10-mg injection of ketamine epidurally. Neither of these patients experienced pain relief. When the preliminary results of the study were examined by our Departmental Research Committee, it was recommended that pain relief from epidural ketamine was inadequate and was excluded from further study.

As Islas et al. suggest, the effects of ketamine appear to be dependent upon the route of administration and the concentration. In higher concentrations, intrathecally the drug appears to have a local anesthetic action (4). We have found, for example, that 2 mg/kg of intrathecal ketamine in dogs produced both sensory and motor blocks. These blocks were of short duration (13 ± 2 min) but could be prolonged by the addition of epinephrine 0.2 ml (41 ± 5 min). Lower concentrations of ketamine administered epidurally probably act primarily as an opiate agonist (4). However, the potency of ketamine is weak compared to that of morphine, and this may limit its usefulness (5,6). Three of our patients had adequate relief of postoperative pain when switched from epidural ketamine to continuous epidural morphine.

Indeed, in comparing the types of patients reported by Islas et al. with those we studied, the greatest difference might have been in the types of surgical procedures and the subsequent expected magnitude of postoperative pain. Islas et al. studied patients who had had primarily minor lower abdominal procedures with excellent postoperative pain relief, whereas we examined major surgical cases with potentially long convalescent periods. Islas et al. state that the placebo effect may explain pain relief in about one-third of patients, but in the absence of a control group this is difficult to determine, as the effect on patients being studied can be quite variable in uncontrolled experiments. Also, because an epidurally administered local anesthetic was used during the patient's surgry, there is no way to assess the contribution of this agent to relief of pain during the postoperative period. We believe that a double-blind comparison with a control group receiving placebo is essential in this type of study as the placebo effect might be quite pronounced. From our own work we believe that the usefulness of epidural ketamine for the relief of postoperative pain is quite limited, and further controlled studies are needed to determine its place in anesthetic practice.

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To the Editor:

We have read with interest the study by Islas et al. (1) regarding epidural ketamine for control of postoperative pain in patients after lower abdominal surgery. We were involved with the original animal experimentation with subarachnoid ketamine (2) and its use in cancer patients suffering from intractable pain (3). The pain relief varied from 30 min to over 6 hours.

Based on our early results (2,3) we studied the use of epidural ketamine in the management of postoperative pain. Unfortunately, we found that epidural ketamine with a dose up to 50 mg did not provide adequate postoperative analgesia (4). The mean duration of pain relief was only 30 min. Our patients differed from those studied by Islas et al. in that our patients all underwent upper, not lower, abdominal surgery. Furthermore, in contrast to the patients studied by Islas et al., our patients were given an anesthetic technique with no narcotic supplementation or local anesthesia.

Our results agree with the results of Bion (5), who evaluated intrathecal ketamine for operative anesthesia in humans. He concluded that intrathecal ketamine can provide anesthesia of sufficient intensity to allow surgery, but that the short duration of surgical analgesia limits the usefulness of this application of ketamine. Hence we have our reservations about the efficacy of epidural ketamine in postoperative pain relief, especially for more painful upper abdominal operations.

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In Response:

In our study, epidurally administered ketamine produced pain relief in all our patients. It is therefore unlikely that the pain relief represents a placebo response; more likely is the possibility that ketamine produced segmental analgesia similar to that produced by epidural opiates (1–3). We did not use a control group because we consider it unethical to use placebos for management of postoperative pain.

As Ivankovich and McCarthy and Brock-Utne suggest, the greatest difference between patients in our study and patients in their experience is the types of surgical procedures, with major surgical cases like hip replacement or thoracotomies needing more aggresive analgesia.

In our experience ketamine administered epidurally to cancer patients in a single bolus provided significantly less pain relief than that provided in postoperative pain patients (less than 3 hours). In cancer pain a continuous infusion may be better than a single epidural injection of ketamine.

Epidural ketamine is not more potent than a local anesthetic or an opioid for major trauma pain or chronic pain, but its analgesic action without side effects makes epidural ketamine adequate for mild pain control in patients with an epidural catheter in place after an epidural anesthesia.

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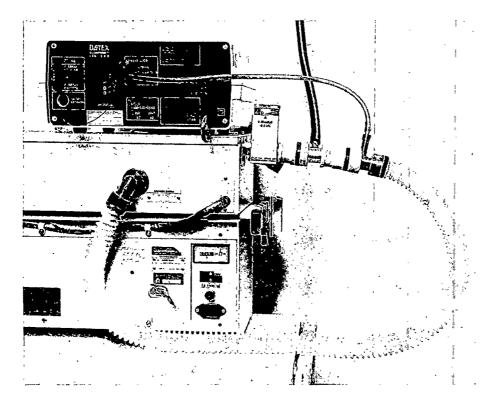
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Operating Room Pollution From "Capnographs"

To the Editor:

We would like to comment on the paper of Lawson and Jelenich (Anesth Analg 1985;64:378) regarding operating room pollution from "capnographs." First, we question their vocabulary, as the etymological derivation of "-graph" is from "graphein," to write or record, which in itself cannot lead to pollution. Rather, it is the process of measuring ("-me-

Figure 1. Technique for prevention of operating room pollution during capnometry.

try," derived from "metrein," to measure) that leads to pollution when using side-stream capnometers. Therefore, the authors should have used "capnometry" instead of "capnograph" in their title and throughout the text. Second, their statement that the manufacturer does not provide standard adaptors for use in scavenging is incorrect. Adaptors have been available in Europe and the US since 1983 (part numbers 86961 and 222014, respectively).

In our hospital, capnometry has been routinely used in all general anesthesias since 1975. The problem of operating room pollution arising from capnometers has been solved by simply connecting the outlet port to the expiratory reservoir of the scavenging system with a length of polyethylene tubing (Fig. 1). According to the recommendations (ISO/TC 121N371), scavenging tubings should be identifiable by the color yellow.

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A Calculus of Suffering

To the Editor:

In his review of my book on 19th-century anesthesia, *A Calculus of Suffering* (Anesth Analg 1985;64:1229), Dr. Leroy

D. Vandam charges me with a litany of supposed errors. In every instance, these allegations are the product either of attributing to me statements I never made, or of apparent unfamiliarity with the source materials.

The review alleges that the book's "supporting statistics are not amenable to verity analysis for the population base from which data are drawn is unknown." This statement is false; the main statistical section in my book presents data for every Massachusetts General Hospital surgical patient, not just a sample. These data were not "drawn" from an "unknown" population base; they included the entire population base. Further, the analysis explicitly compares the surgical patient population to each of three additional controls: all patients with similar admitting conditions; all patients in the hospital; and all residents of Boston.

The reviewer claims I state "that the anesthesia death rate in 1970 was one in 2000 operations." In fact, my book makes no such statement. I do report the historical fact that Beecher and others made such estimates, but I explicitly distinguish my assessment of these dangers from Beecher's. Documenting the existence of anesthesia's critics (past or present) is not the same as agreeing with them.

In saying that I imply "Morton was the first to give anesthesia," Dr. Vandam misreports not only my specific words, but the entire subject of the book. I wrote that Morton "first demonstrated" surgical ether anesthesia. ("Demonstrate: to show or prove publicly"—*Webster's Dictionary.*) I selected those words precisely because I did not intend to write yet another volume in the endless and fruitless debate over who discovered anesthesia first. Dr. Vandam

tells your readers that my book was motivated by "a fascination with the 'discovery' of anesthesia." In fact, the book never even mentioned the "discovery." Rather, the book is a study of the uses and results of anesthesia in the first generation after it was introduced.

The reviewer also repeatedly faults my one-paragraph description of Morton's demonstration. Unlike most previous writers, I based my brief account of this operation in part on the actual Massachusetts General Hospital patient record, rather than relying entirely on recollections published months or decades later. While my book discussed the shortcomings of this document, what Dr. Vandam refers to as my "gaffes" are in fact fully supported by this patient report; a source whose existence he never mentions.

In addition to these and other erroneous accusations of error, the review lists a number of "demurs" that can only be characterized as illogical: "Can one assert that industrialization of society in those times increased anesthetic and surgical mortality, or was it the still unsolved specter of infection? Did the demand for operations increase with the advent of anesthesia, or were the operations merely of the same superficial kind?" In both cases, the reviewer demands a choice between two nonexclusive options. My book spends a full chapter demonstrating that industrialization increased surgical mortality by increasing the number of as-yet-unpreventable infections; and that after anesthesia, people did a lot more of the same old types of surgery.

I have always sought to promote mutual cooperation between anesthesiologists and historians in the difficult effort to understand anesthesia's past, and I respect Dr. Vandam's contributions to this field. I have never before participated in a public dispute with a reviewer, but I believe the extent of Dr. Vandam's errors and misrepresentations requires a response.

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Prolonged Myoclonus after Etomidate Anesthesia

To the Editor:

Drs. Laughlin and Newberg are incorrect when they state that the occurrence of myoclonus on emergence from etomidate anesthesia has not been previously reported (1). In 1977 Kay and Rolly (2), in a study of intravenous anesthesia using etomidate, stated that "in the other six patients, however, myoclonic movements persisted even after full recovery of consciousness, in three patients accompanied by marked restlessness and mental agitation. The course tremor was most obvious when purposeful movement was attempted, but in one patient spontaneous myoclonia persisted for more than half an hour." Similar observations were published in a later study of etomidate for major surgery (3).

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Book Reviews

Anaesthesia in the Elderly
Harold T. Davenport. New York: Elsevier Science
Publishing Company, Inc., 1986, 200 pp, $19.50. (Orders
outside the US to Heinemann Publishers, London.)

Anaesthesia in the Elderly is a single-authored, 13-chapter,
paperbound volume that attempts to integrate relevant in-
formation on gerontology with the author's extensive clin-
ical observations regarding this type of patient. This ap-
proach achieves evenness of style and pace, but also has
an obvious drawback: lack of specialized expertise in the
many component areas that must be discussed in a volume
of this title. This is a nice book, and is, in general, a com-
petent overview, but it leaves the serious reader unsatisified
because it fails to provide stimulating and convincing an-
swers or hypotheses regarding the mechanisms by which
aging alters anesthetic requirements and the elderly pa-
tient's response to stress in the perioperative period.

There is some effort to incorporate recent data from the
field of gerontology, but they are presented uncritically, and
thus this book is essentially an anecdotal monograph. This
impression is further enhanced by the lack of specific ref-
erences within the text itself. Thus the reader is obliged to
review the entire list of references that follows each chapter
in order to determine the likely source of a statement in
question. I found numerous errors in authorship and title
for many of the references.

Those who read Dr. Davenport's *Anaesthesia in the Elderly*
will find interesting information on practical management
and assessment of elderly patients, but they will learn little
about the neurophysiology of aging or the mechanisms by
which the distribution and metabolism of anesthetic drugs
are altered. Fortunately, these topics are well covered in
other recent books of this type, such as *Anesthesia in the
Geriatric Patient* (Grune and Stratton, 1984) and *Geriatric
Anesthesia: Principles and Practice* (Butterworth's, 1986). Gen-
eral descriptions of neurologic and physical changes that
occur with age and the types of illnesses and procedures
common in these patients occupy chapters 1, 2, 4, 7, 8, and
9 of this volume, and much of the remaining chapters con-
tain little information that is new or truly unique to the
elderly. Research into areas of gerontology with implica-
tions for anesthesia is moving rapidly. The definitive vol-
ume appropriate for the title of this book remains to be
written.

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Anesthesia and Coronary Artery Surgery
Sait Tarhan, ed. Chicago: Yearbook Medical Publishers,
Inc., 1984, 381 pp, $69.95.

In the last five years several books dealing with anesthesia
and heart surgery have been published, but this is the first
one that deals exclusively with anesthesia and coronary
artery surgery. Twenty-three anesthesiologists and car-
diologists participated in this publication; all of them are or
were on the Mayo Clinic staff. Therefore, one would expect
a good part of this book to reflect the practice of cardiac
anesthesia in this reputable center.

Similar to other books with several contributors, there
is redundancy and repetition; subjects such as myocardial
oxygen balance and myocardial preservation are discussed
in separate chapters and are included in many others. The
book reviews many subjects such as monitoring and ar-
rhythmias, and anesthetics, that are not exclusively related
to anesthesia and coronary artery surgery. On the positive
side, the repetition and reviews allow each chapter to stand
on its own, providing adequate information about the main
subject discussed or about related issues.

The book deals elaborately with the pathophysiology of
the coronary circulation; coronary artery disease; coronary
angiography; and recent therapeutic measures for myo-
cardial ischemia, including the use of thrombolytic therapy,
PTCA, and emergency coronary artery surgery for treat-
ment of acute or chronic ischemia. These subjects as they
apply to the practice of anesthesia are well reviewed and
summarized in simple language.

The chapter about anesthetic agents discusses muscle
relaxants, as well as currently used, obsolete, and future
drugs related to anesthesia. So far, many of these agents,
such as gallamine, carfentanil or hydromorphone, have no
application in coronary artery surgery. However, in only
30 pages, this chapter provides an excellent review of opioids,
inhalational and intravenous anesthetic agents, and muscle
relaxants, with special emphasis on their cardiovascular ef-
fects. This chapter alone has over 300 references, including
the very recent and most relevant.

Of particular value is the chapter about anesthesia for
noncardiac surgery performed on patients with coronary
artery disease. The editor was one of the first to emphasize
the risks of preoperative MI in patients with coronary artery
disease who are undergoing surgery; so, as one might ex-
pect, this chapter has a comprehensive review of such risk
factors, summarizing and discussing almost all prior pub-
lications in this area. It also extensively reviews the merits
of general, local, and regional anesthetic techniques. How-

ever, since the book is identified with Mayo Clinic anesthesiologists, it would have been appropriate to dedicate a section to anesthesia management techniques at Mayo Clinic to reflect the authors' large experience.

This book is well organized and clearly written. It has many valuable clinical tips and reviews, but one of its most important features is the large number of references; these exceed 2200.

With the increased popularity of coronary artery surgery—over 150,000 per year in the US—and the increased awareness of the possible risk of anesthesia to patients with coronary artery disease, this book provides an important service. It will serve as a good text and a ready reference to answer many questions for the practicing anesthesiologist as well as the trainee.

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Anesthesia (second edition)

Ronald D. Miller. New York: Churchill-Livingstone, 1986, 2419 pp, $150.00.

The first edition of this book became known as the definitive textbook for anesthesia in North America. With the addition of 22 chapters and 886 pages, the scope of this book has been substantially increased. Many chapters from the previous edition have been revised and improved. New inclusions in this book center on knowledge pertinent to basic anesthesia as well as to the administration of anesthesia in complicated disease states. Specifically, scientific foundations such as pharmacologic principles, physics, computors, statistics, and physiology are addressed. Consideration of anesthetic interrelations with cardiac dysrhythmias, carotid endarterectomy, liver disease, and renal impairment are also new topics specifically addressed in this book. Literature references are generously utilized and a major strong point for the book. With 70 American authors, the standard of care of American anesthesiology practice is reflected quite accurately, although an international scope is lacking.

Unfortunately, there is little use of cross-referencing of headings within the index. Many subjects are not indexed, and some index entries do not give all the relevant page numbers. The paramount example is that under "Cholinesterase Inhibitor," not once is any page from chapter 27, "Pharmacology of Muscle Relaxants and Their Antagonists," listed in the index. Because of the large number of authors, many topics are discussed in more than one chapter, but the index disregards this fact. The use of boldface or cursive print to direct reference search through the index is not utilized to any degree. Printing errors can be found (some of which were present in the first edition) but are not overwhelming. A number of new drugs are included in the discussion.

This book could have been less bulky and less expensive had it been brought out in two, rather than three, volumes. Although this work addresses the substance of anesthesia as well as most clinical interfaces, the need for ancillary literature must be recognized. This becomes extremely obvious in the superficial discussion of dysrhythmia, where only five drugs are *briefly* presented in the chapter on this subject. Allocation of space in the text is not always optimal: one third of a page is used to discuss the moot point of whether the bevel of the standard IV cannula should be up or down upon insertion. The more important relative topics such as inadvertent arterial cannulization, vein anatomy, and practical aspects are neglected. Nonetheless, the advantages of access to the information contained in this book outweigh any disadvantages noted. This book remains a prerequisite for any departmental library and can be highly recommended to all concerned with the practice of anesthesia. The possession of the first edition of this work will be a substantial deterrent to the purchase of the second edition, as cost effectiveness may well dictate the purchase of other supportive texts, rather than this second edition.

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Advances in Anesthesia (volume three)

R. K. Stoelting, P. G. Barash, and T. J. Gallagher. Chicago: Yearbook Medical Publishers, 1986, 403 pp, $55.95.

This book consists of ten chapters which update topics of interest to the anesthesiologist. Some subjects are new to the reader, while other chapters present novel concepts or provide additional knowledge in already familiar areas. The material in the book is usually concise, researched thoroughly, and referenced extensively. References through 1984 are cited. Patient management discussions are only occasionally dogmatic. Each chapter is complete enough to stand alone, but all are similar enough in style to fit within the same book.

The first chapter on organ transplantation is highlighted by the discussion of orthotopic liver transplantation based on the author's experience at Pittsburgh. The next sections on local anesthetic toxicity and perioperative hemostatis are written in a scholarly manner by experts. The next topic compares the pharmacology of induction agents. Reasons are presented for the 50-year prevalence of thiopental. The chapters on allergy and anaphylaxis, potassium homeostasis, and a new look at "pressors" begin with thorough explanations of basic principles, followed by clinicially oriented applications. Some readers may find that the discussion of preoperative hypokalemia is weighted toward the replacement side. The section on anesthesia for vaginal delivery and cesarean section presents recent developments

in choice of local anesthetic. Prearrest factors, outcome, and mechanisms of CPR are presented in quality fashion and are topics not usually found in the anesthesia literature. This dispels the worry that the first author of the chapter on cardiopulmonary resuscitation is an intern in medicine. The final section on urologic anesthesia covers renal failure, renal transplantation, and transurethral resection of the prostate. Anesthesia for lithotripsy is too current for this book and must await publication of future volumes.

There are an adequate number of illustrations and good use of tables and graphs. Some discussions of basic principles are a bit long. Because each chapter can be read independently, repetition occurs. Local anesthesia toxicity is covered to some extent in three chapters and anesthesia for renal transplantation in two. A few minor inconsistencies and errors exists. F_{IO_2} is defined as "forced inspiratory oxygen" and MAC as "maximum allowable concentration." Grammatical errors are almost completely confined to the occasional split infinitive. Typographic errors ("ug" for "mg") and misspellings are rare.

Volume 3 of *Advances in Anesthesia*, as in the first two volumes, covers material found in between standard texts and journals. This book will be taken from the shelf as the topics presented are sought by the resident and practicing anesthesiologist. They will find well-researched and informative material.

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Current European Anaesthesiology (volume 1)
R. M. Jones, H. Bergmann, J. Lassner, J. C. Olteni, and D. Thomson, eds. Plymouth, England: John Wiley and Sons, 1985, 297 pp, $24.50.

This English language collection of 170 abstracts, each one followed by an expert comment or review, is the Yearbook of the European Academy of Anaesthesiology. The articles, mostly clinically oriented, are selected from 21 European journals, the majority of them devoted to anesthesiology. The journals come from 15 different countries where the primary language of most of these journals (and of most of the reviewers) is not English. Therefore, the translating, reviewing, and editing that underlie this composition represent considerable effort.

The abstracts have been placed into five groups: 1) pharmacology, 2) medical problems, 3) clinical practice, 4) equipment and monitoring, and 5) resuscitation and intensive care. This classification has necessitated some arbitrary assignments, e.g., the paper on echocardiographic monitoring of ventricular performance after thiopentone perhaps would have been better placed under "Monitoring" instead of "Resuscitation and Intensive Care." Each abstract averages about 400 words in length, and most appear to have

been prepared by the editoral board. The reviews tend to be shorter and are usually, though not always, based on both the abstract and the original paper. However, the reviews vary widely; some are lengthy discourses analyzing the paper, its methodology, the statistical techniques used, and the conclusions. Others are short. A particularly pithy one was the comment that followed the multiauthored paper entitled "Receiving Station for Brain Death Cases and Organ Transplantation." The complete review was, "The long list of names under the title of this paper shows that it is not easy to keep doctors working for long in such a facility!"

The editorial board requested the editors of the various journals to suggest articles for inclusion. This must explain, at least in part, the variety of topics covered: from working conditions for intensivists in the east to epidural fentanyl in the west; from poisoning with tricyclic antidepressants in the north to misplaced central venous lines in the south; from the use of premixed nitrous oxide at sea level to provide analgesia for dentistry to the use of premixed nitrous oxide at 3300 feet to provide analgesia after trauma; from 14 papers about opioid analgesics postoperatively to one about using enflurane to provide analgesia during labor. The book makes interesting reading and provides a variety not available from the handful of journals scanned by most practitioners.

There are major problems in compiling a book of this nature, some of which are evident (e.g., the editors, and through them the readers, have to tolerate at least nine different methods of measuring pressure). The variety presented to the readers also appears to stem partly from failing in translation or transcription. Thus the abstract on page 21 describes satisfactory preoperative sedation with rectal flunitrazepam, 0.03 mg/kg. However, the two preceding abstracts conclude that rectal flunitrazepam (0.33 and 30 mg/kg) did not cause adequate drowsiness. These are remarkable findings for doses which, as printed, appear to be tenfold and one thousandfold larger, respectively.

The index is incomplete and inconsistent. None of the three papers referred to above appears in the index under flunitrazepam; the drug is omitted from the index even though it appears in all three titles. Three abstracts that appear later in the book provide further illustrations: "Noninvasive Technique for Monitoring Lung Vascular Permeability in Man" (p. 271); "Surfactant Replacement in Neonatal and Adult Respiratory Distress Syndrome" (p. 278); and "Transthoracic Electrical Impedance to Control Spontaneous Respiration with Continuous Positive Airway Pressure (CPAP)" (p. 280). Not one of these papers is indexed under any of the words in their titles. The first paper involves a measurement technique but is indexed under "Adult respiratory distress syndrome"; the second which has "Adult respiratory distress syndrome" in the title is indexed under "Lung"; and the third paper appears only under "Measurement techniques," a group that could have usefully included the first paper.

This reviewer's initial reaction was enjoyment of the va-

riety as well as interest in the interaction between abstract and review. Used as a source of stimulation and as an opportunity to get an overview of European clinical research in anesthesia, these favorable reactions persist and are not marred by the deficiencies noted above. Future volumes will undoubtedly appear and will be welcomed, particularly so if they have a more comprehensive index and, possibly, a greater number of groups for the papers.

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The Management of Postoperative Pain
Margaret E. Dodson, ed. Baltimore, MD: Edward Arnold, 1985, 274 pp, $49.95.

Despite the recognition that postoperative pain is a significant problem for patients, few texts have been written on the management of postoperative pain. This book represents a significant advance in that it describes the multitude of factors that affect postoperative pain, reviews the methods applied to treatment of postoperative pain, summarizes most of the important clinical studies in postoperative pain of the last 30 years, and provides suggestions on patient management both for general and specific situations.

The book is multiauthored, but most of the chapters are written by Dr. Dodson which allows the book to have continuity of style and content. The introductory chapters are a well-referenced summary of the clinical research done in the field of postoperative pain management, better than most review articles published to date. The chapter on pathophysiology and natural history of postoperative pain is an excellent review of clinical work done from 1950 to 1980, which continues to be overlooked in texts on postoperative pain management.

The chapters on analgesic drugs contain pharmacologic information readily available in most standard texts, but further describe how these drugs have been studied in the management of postoperative pain. The discussion of clinical studies of narcotic administration suggest that the regular administration of a narcotic dose is as effective as newer, more expensive patient-controlled analgesia and technically more difficult epidural administration. Recent research on clinical applications of epidural opiates is discussed. However, the guidelines for the use of epidural morphine are based on limited clinical experience and are too conservative to allow effective use of these agents in the clinic. Another shortcoming of the book is in its minor inconsistencies in the discussion of transcutaneous electric nerve stimulation. The overview places TENS in its proper context, that of an unproven modality, but later references to TENS suggest its efficacy.

Nonetheless, the book represents an important advance in providing a well-referenced discussion of this exceedingly complex, difficult topic. The author and contributors

are to be commended for providing a useful reference source for anesthesiologists, surgeons, and allied personnel that will aid and improve the quality of postoperative care.

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Guidelines in Clinical Anaesthesia
Peter Hutton and Griselda Cooper. Oxford: Blackwell Scientific Publications, 1985, 403 pp, $32.95.

Each chapter in *Guidelines in Clinical Anaesthesia* addresses the common diseases of a particular organ system. A discussion of helpful techniques of physical diagnosis (which is the strong point of the book) and a brief commentary on relevant anesthetic considerations are integral to each chapter. The book's format is excellent. The typographical design underscores the superior organization of the information and makes it easy for the reader to find specific sections quickly.

It is unfortunate that very little emphasis is given to in-depth discussions of anesthetic techniques and agents or monitoring techniques. The depth and breadth of the information is appropriate for the medical student, but is much too superficial for the anesthesia resident preparing for board examinations. This British import must therefore be used in conjunction with other texts more oriented to anesthetic management if it is to be of value to the board examination candidate's study program.

Many unsubstantiated personal opinions and controversial statements are made without sufficient evidence of their veracity either in the text or in the bibliography. Many of these concepts are based on clinical impressions and not necessarily on documented fact. (To be fair, however, the authors state that this is their intent—they did not set out to write a reference source book.) This may be more appropriately published in an anesthesia handbook but is too subjective for a preparatory text for board examination.

As stated by the authors in the preface, this book is "intended primarily for anaesthetists in training and particularly for those preparing for the examinations of the Faculty of Anaesthetists." In all respects but this, the authors have accomplished their stated goals.

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Spinal Injury (second edition)
David Yashan. Norwalk, CT: Appleton-Century-Crofts, 1986, 527 pp, $69.95.

This work covers multiple aspects of a subject of great medical and economic importance. The cohesiveness of orga-

author providing up-to-date information in all areas of this complex subject. The book is anatomically oriented and aimed at the surgeon in training. It would be a reasonable addition to the reference library for the anesthesiologist who frequently deals with patients undergoing spinal surgery or who have suffered spinal trauma.

The table of contents is robust, with a reasonable progression from the history of treatment of spinal injury to anatomy and physiology, ending with a discussion of associated injuries and systemic complications of spinal injury. The book contains many simple and logically placed figures. The numerous black and white photographs and x-rays complement the text well. The chapter concerning pathology is particularly well-organized with a clear presentation of the spectrum of spinal injury.

The anesthesiologist will find the parts of the book concerning anesthesia and intraoperative monitoring simplistic but accurate. There is surprisingly little information about intraoperative monitoring of spinal cord function. Unfortunately, little information is provided concerning neurologic intensive care or newer imaging techniques such as nuclear magnetic resonance.

In summary, this work is a useful reference book which provides an accurate but simplified discussion of all aspects of spinal injury. Numerous references are provided in each chapter; they are fairly up to date.

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Anesthesia for Ambulatory Surgery

In a relatively short period of time, the government, followed by other third-party carriers, has mandated that to be eligible for reimbursement of unit costs, certain operative procedures must be done on an ambulatory basis. Prior to this, many in the health care professions were too conservative to provide surgical care on this basis, but it is now an established fact.

Initially this venue for surgical procedures was reserved for only limited procedures on physically fit patients of ASA physical status I or II. For many reasons, the list of procedures to be done on this basis is currently expanding. Some predict that up to 40-60% of the total surgical procedures done in this country will be done on an ambulatory, in-and-out, same-day, come-and-go, or outpatient surgery basis. As the title of the first chapter of this book states, "The Future is Now."

Anesthesia for Ambulatory Surgery was written, as stated, by the editor "to provide anesthesiologists [and for that matter, anyone else interested in this topic] with the information needed to understand and meet the challenges."

The ten chapters of this book give the reader the benefits of the considerable experience of acknowledged experts in with patient selection, anesthesia techniques, problem-solving, and complications. In addition, there are some novel approaches, as found in the chapter entitled "In the Real World." In this chapter, actual cases seen in ambulatory care facilities are described with known authorities discussing the problems posed, followed by a response by the chapter authors.

There is an excellent chapter dealing with "Legal Implications," which is of significance to all of us involved in patient care in any specialty of medicine. The chapter dealing with a "Successful Facility" covers planning, marketing, and the fundamentals of a successful unit.

This book can be easily read, and does not suffer from the uneven presentation often associated with multi-authored books. The tables are easily understood and appropriate; they are sure to be reproduced. The illustrations are sharp and clear except for the two figures on page 198, which were fuzzy in my copy.

A glance at current meetings, agendas, and articles attest to the importance of ambulatory care. The editor and authors involved in this book have set a standard in this field that will be difficult to match. For all of us involved in this area of subspecialization, this book is recommended. For those just starting, it should be obligatory.

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Acid-Base Regulation and Body Temperature

Each year in the US, hypothermia is used in about 200,000 cardiac operations. Yet the proper management of acid-base balance when body temperature is decreased is uncertain. This book attempts to remedy this.

The volume is divided into two parts. The first consists of four chapters that discuss the acid-base changes and their consequences during hypothermia. A brief introduction is followed by an excellent description of the concept "alphastat regulation." It explains how the control of protein function by adjustment of histidine imidazole groups bearing a proton is the central objective of acid-base regulation. The fraction of the histidine imidazoles in the unprotonated form is known as α. When $pH - pK_{im}$ remains constant, α is also constant—hence "alphastat regulation." Such regulation occurs not only in warm-blooded animals but also in cold-blooded vertebrates as their daily temperature changes. From a practical point, a constant α can be achieved by measuring the pH and PCO_2 of a blood sample at 37°C and by managing the patient as though he were at normal body temperature. This chapter is followed by a description of acid-base changes during hibernation, which do not depend upon constant α but upon constant pH. The general concepts conclude with a description of the benefits

ing pH gradients across the mitochondrial membrane.

These excellent descriptions are followed by disappointing clinical applications. The chapter describing acid–base status and hypothermic cardiopulmonary bypass is long on opinion but short on facts. It is followed by a description of hypothermia and acid–base regulation in infants, which is interesting more for its description of anesthetic methods than any advances in acid–base theory. Finally, the book ends with a brief description of a study that examines the hemodynamic aspects of puppies during hypothermia. Somewhat surprisingly, cardiac output and renal and cerebral perfusion are better preserved when the animals are made more alkalemic than with alphastat regulation. The reader is left in the air.

Clearly, the purpose of this book is well-justified. There is much to learn from comparative physiology that is relevant to the management of acid–base balance during hypothermia in humans. However, studies in humans lag behind those in animals.

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ERRATA

Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. Pharmacokinetics of Inhaled Anesthetics in Humans: Measurements during and after the Simultaneous Administration of Enflurane, Halothane, Isoflurane, Methoxy-flurane, and Nitrous Oxide. Volume 65, Number 6, June 1986.

Page 577, legend to Figure 1, lines 5–6
TO READ . . . 230-min
CHANGE . . . 2- and 4-day

CHANGE . . . longarithmic
TO READ . . . logarithmic

Page 578, legend to Figure 2, line 6
CHANGE . . . 230-min
TO READ . . . 2- and 4-day

One agent has inspired a new way of looking at surgical muscle relaxation.

TRACRIUM® INJECTION
(atracurium besylate)
Intrinsically predictable, uncommonly flexible

◆ Predictable because it doesn't accumulate.

Equal maintenance doses of Tracrium, repeated at equal time intervals during surgery, have no cumulative effect on recovery time.

Once recovery begins following the last administered dose, it is relatively rapid and independent of the total dose. Thus, you need not calculate progressively smaller doses of Tracrium for repeat administration. Recovery is more consistent and predictable.

◆ Metabolized independent of liver or kidney function.

Tracrium® Injection (atracurium besylate) is not dependent on kidney or liver function for elimination. It is inactivated by two nonoxidative pathways:

New Use: Infants from one month of age

TRACRIUM® INJECTION
(atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short-term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to stimulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:

Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Adults: A Tracrium dose of 0.4 to 0.5 mg/kg (1.7-2.2 times the ED_{95}), given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. No Tracrium dosage adjustments are required for patients with renal disease.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended for adults following the use of succinylcholine for intubation under balanced anesthesia. Further reductions may be desirable with the use of potent inhalation anesthetics. The patient should be permitted to recover from the effects of succinylcholine prior to Tracrium administration. Insufficient data are available for recommendation of a specific initial Tracrium dose for administration following the use of succinylcholine in children and infants.

U.S. Patent No. 4179507   Printed in U.S.A.

TRACRIUM INJECTION
(atracurium besylate)

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Anesthesia and Analgesia

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Forane® (isoflurane)
The Versatile Anesthetic

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Forane® (isoflurane)

Forane® (isoflurane)
The Versatile Anesthetic

A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]

Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery (Adapted from Hess et al[3]).

- ●○ —·—·— Pretreatment (fentanyl, flunitrazepam, pancuronium)
- ● ———— Treatment with isoflurane
- ○ — — — — Treatment with halothane

Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

Post-laparoscopy Nausea (N) and Vomiting (V)		
Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N_2O, O_2	37	23 (62%)*
isoflurane, fentanyl, O_2	20	6 (30%)
isoflurane, O_2	20	5 (25%)

Adapted from Alexander et al[8]   *p<0.05

References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981.   3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983.   4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971.   5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709.   6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981.   7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981.   8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

For complete use information, please see following page.

Forane®...a product of original Anaquest research
(isoflurane)

Forane®...The Versatile Anesthetic
(isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION: FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:

$$
\begin{array}{ccccccc}
 & F & & H & & F & \\
 & | & & | & & | & \\
F & - C & - C & - O & - C & - H \\
 & | & & | & & | & \\
 & F & & Cl & & F &
\end{array}
$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where:} \quad A = 8.056$$
$$B = -1664.58$$
$$T = °C + 273.16 \text{ (Kelvin)}$$

Partition coefficients at 37 °C
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8

Partition coefficients at 25 °C - rubber and plastic
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5

Purity by gas chromatography — >99.9%

Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C — None

Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C — Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY: FORANE (isoflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N₂O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO₂, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE: FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS: Known sensitivity to FORANE (isoflurane) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS: Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS: General: As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N₂O. See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (hot canister). PaO₂ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS: Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION: Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:
  a) vaporizers calibrated specifically for isoflurane;
  b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\% \text{ isoflurane} = \frac{100\,P_V\,F_V}{F_T\,(P_A - P_V)}$$

where:
P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED: FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0117 Revised 5-84

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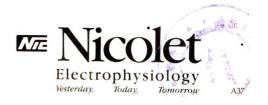
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